

# **Flesh, Blood, Sex and Consumption: Applied Epidemiology in Victoria**

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Master of Philosophy (Applied Epidemiology)  
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Health  
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## Originality statement

I declare that to the best of my knowledge the content of this thesis is my own work. Any assistance or contribution received from others has been explicitly acknowledged. It has not been previously submitted for any other degree or for any other purposes.

A handwritten signature in black ink, appearing to read 'Shaun Peter Coutts', written in a cursive style.

Shaun Peter Coutts

November 2019



## Acknowledgements

I would like to acknowledge the many people who have helped me out along the way.

**Colleen Lau** has been a brilliant academic supervisor throughout, always willing to offer the kind of support, advice and general academic and epidemiological wisdom that has made all the difference to the quality of this thesis. Thanks also to my co-supervisor **Emma Field** for her insightful and challenging comments on my works-in-progress.

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## Acronyms and Abbreviations

ACCESS - Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood-borne Viruses and Sexually Transmissible Infections

AHPPC – Australian Health Protection Principal Committee

ANU – Australian National University

BBV – Blood-borne virus

BG trap – BioGents mosquito trap

BCG - Bacille Calmette-Guérin vaccine

BU – Buruli ulcer

CDC – Centers for Disease Prevention and Control (USA)

CDES – Communicable Disease Epidemiology and Surveillance

CDNA – Communicable Disease Network Australia

CDPC – Communicable Disease Prevention and Control

CI – Confidence interval

CNC – Clinical nurse consultant

CRF – Circulating recombinant form

CSIRO – Commonwealth Scientific and Industrial Research Organisation

CXR – Chest X-ray

DEC - Diethylcarbamazine

DHHS – Department of Health and Human Services (Victoria)

DOT – Directly observed therapy

FETP – Field Epidemiology Training Program

HBV – Hepatitis B virus

HCV – Hepatitis C virus

HIV – Human immunodeficiency virus

HR – Hazard rate

HREC – Human research ethics committee

IDA – three-drug MDA regimen of Ivermectin, DEC and Albendazole.

IGRA – Interferon-gamma release assay

IQR – Inter-quartile range

LF – Lymphatic filariasis

LTBI – Latent tuberculosis infection

MAE – Master of Philosophy (Applied Epidemiology)

MDA – Mass drug administration

MDU – Microbiological Diagnostic Unit Public Health Laboratory

MDR-TB – Multi-drug resistant tuberculosis

MIRU-VNTR - Mycobacterial Interspersed Repetitive Unit Variable Number Tandem Repeat

MRL – Mycobacterium Reference Laboratory

MSM – Men who have sex with men

MX – Molecular xenomonitoring

NNDSS – Nationally Notifiable Diseases Surveillance System

PBS – Pharmaceutical benefits scheme

PCR – Polymerase chain reaction

PHESS – Public Health Event Surveillance System

PrEP – Pre-exposure prophylaxis

PSU – Primary sampling unit

SaMELFS – Surveillance and Monitoring to Eliminate Lymphatic Filariasis and Scabies

SDK – Secure Data Kit

SNP – Single nucleotide polymorphism

STI – Sexually transmissible infection

TB – Tuberculosis

TBD – Tuberculosis disease

TST – Tuberculin skin test

URF – Unique recombinant form

VIDRL – Victorian Infectious Diseases Reference Laboratory

VTP – Victorian Tuberculosis Program

WGS – Whole genome sequencing

WHO – World Health Organization

XDR-TB – Extensively drug-resistant tuberculosis

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## Abstract

In this thesis I present the key projects and activities completed as part of the Australian National University's Master of Philosophy in Applied Epidemiology (MAE) program during my candidature in 2018-2019.

During my candidature I was based in the Communicable Disease Epidemiology and Surveillance (CDES) unit at the Victorian Department of Health and Human Services (DHHS), and the Surveillance and Evaluation group at the Burnet Institute in Melbourne, Victoria, Australia. I completed four major projects across these two organisations, as well as being involved with a range of other infectious disease surveillance and research activities.

At DHHS, I was involved in the investigation of a large, complex cluster of tuberculosis cases in a Pacific Island cultural community. This three-year investigation was one of the largest tuberculosis cluster investigations ever undertaken by the Department of Health and Human Services and the Victorian Tuberculosis Program. The epidemiological side of the investigation in which I was involved utilised epidemiological, social-location and genomic data to better understand transmission within this complex cluster.

I also conducted an epidemiological study of delays in patient presentation and diagnosis for Buruli ulcer in Victoria. Given the current lack of effective interventions to reduce disease transmission in Victoria, prompt diagnosis and treatment are critical to minimise the impact of the disease. The study aimed to characterise and identify factors influencing presentation and diagnosis delays in patients notified to DHHS between 2011 and 2017 to better inform public health messaging for the public and medical practitioners. The study was published in the *Tropical Medicine and Infectious Diseases* journal in July 2019 and presented at the National Centre for Epidemiology and Population Health Seminar Series in February 2019. The published article forms the body of the relevant chapter in this thesis.

At the Burnet Institute I completed an evaluation of the Australian Collaboration for the Coordinated Enhanced Surveillance of Blood-Borne Viruses (BBVs) and Sexually Transmissible Infections (STIs) (ACCESS), a sentinel surveillance system for STIs and BBVs funded by the Australian Government Department of Health to expand nationally between 2016-2019. Based on the outcomes of the evaluation, I made several recommendations to improve the operation of ACCESS during the next potential funding period. The findings of this evaluation were provided to the Australian Government Department of Health as part of the final project deliverables for the funding period.



My data analysis project at the Burnet Institute examined the epidemiology and subtype diversity of HIV-1 in newly-arrived Asian-born and Australian-born men who have sex with men (MSM) populations in Victoria using routinely-collected surveillance and subtyping data. Understanding and addressing HIV transmission in the newly-arrived Asian-born MSM population is increasingly important in Victoria, with both the population and the proportion of HIV notifications from the population increasing in recent years. This study was presented as an invited oral presentation at the International Union Against Sexual Transmitted Infections Asia-Pacific Conference in Shanghai, China in October 2019. A manuscript based on this project has been submitted for review to the peer-reviewed journal *Sexual Health* – this late-draft manuscript is presented as the body of the relevant chapter in this thesis, in the format required by the journal.

The appendices to the thesis include summaries of other program requirements or achievements completed outside these four major projects. I developed public health communications materials for a non-scientific audience in the form of participant information for the NHMRC-funded *Beating Buruli in Victoria* case-control study. I completed three teaching activities; a lecture on data visualisation, a session on the basics of social network analysis for infectious diseases, and a “lesson from the field” on tuberculosis cluster and outbreak investigations. Finally, I present a short summary of my involvement as a team leader/epidemiologist in the Surveillance and Monitoring to Eliminate Lymphatic Filariasis and Scabies in Samoa (SaMELFS Samoa) mosquito survey and molecular xenomonitoring study, for which I travelled to Samoa in June 2019.

Through the completion of the projects and activities recorded in this thesis, I have clearly demonstrated the core field epidemiology training program competencies, and accumulated knowledge and experience that will no doubt serve me well in the future.



## Chapter I

### Summary of Field Experience

#### Introduction

For the duration of the 2018-2019 Australian National University (ANU) Master of Philosophy (Applied Epidemiology) program (MAE) I was based at the Victorian Department of Health and Human Services and the Burnet Institute in Melbourne, Victoria, Australia.

The Victorian Department of Health and Human Services (DHHS or the Department) is a state government department responsible for a broad range of public services including public health, public hospitals, ambulance services, child safety, mental health and sports. The Department currently provides advice to four government ministers and directly employs over 11,000 staff throughout Victoria.

My placement at the Department was with the Communicable Disease Epidemiology and Surveillance unit (CDES) in the Health Protection branch, based at 50 Lonsdale Street, Melbourne. Managed by Dr Nicola Stephens (up until February 2019, thereafter by MAE alumnus Lucinda Franklin), CDES is responsible for the collection and analysis of communicable disease surveillance data in Victoria, primarily through the operation of a notifiable disease surveillance system.

CDES works closely with other units in the Communicable Disease section (including Communicable Disease Investigation and Response and Immunisation) in the collection, interpretation and use of surveillance data for public health action. Epidemiologists from the section also increasingly provide support for non-communicable disease epidemiology throughout the branch including elevated blood lead, epidemic thunderstorm asthma, heat health and anaphylaxis.

Dr Ee Laine Tay was my primary field supervisor at DHHS. Ee Laine is a medically-trained epidemiologist and completed the MAE in 2012-13 through a joint placement at the Department and the Victorian Infectious Diseases Reference Laboratory (VIDRL). Ee Laine is primarily responsible for the surveillance of the notifiable mycobacterial diseases; tuberculosis, Buruli ulcer and leprosy.

The Burnet Institute (Burnet or the Institute) is an independent, not-for-profit medical research organisation that aims to link laboratory and field-based medical research to practical public health action both in Australia and overseas. Headquartered at 85 Commercial Road,

Melbourne, the institute also maintains international offices in China, Laos PDR, Myanmar, Papua New Guinea and Zimbabwe.

My placement at the Burnet Institute was with the Surveillance and Evaluation group, which operates under the Disease Elimination program and the Public Health discipline. The objectives of the group are:

- Managing, developing and refining innovative surveillance systems to better understand the transmission of HIV, blood borne viruses (BBVs) including hepatitis B and C and sexually transmissible infections (STIs).
- Undertaking evaluation projects to examine the effectiveness of policy and initiatives aimed at reducing the transmission and impact of communicable diseases, including BBVs and STIs.
- Integrating findings from surveillance, epidemiology and research to inform policy and practice to prevent the transmission of diseases such as HIV and other STI transmission.

My primary field supervisor at the Burnet Institute was Carol El-Hayek, Head of Surveillance and Evaluation. Carol is an experienced epidemiologist with a strong background in HIV, BBV and STI epidemiology, and an Adjunct Research Fellow with Monash University’s School of Population Health & Preventive Medicine.

### Core Applied Epidemiology Competencies

As a field epidemiology training program (FETP), the MAE program focuses on the development and demonstration of the core competencies expected of a field epidemiologist.

The demonstration of these competencies during my candidature, and their documentation in this thesis, is summarised below.

Core competency	Chapter II	Chapter III	Chapter IV	Chapter V	Appendices
Investigate an acute public health problem					
Analyse a public health dataset					
Evaluate a surveillance system					
Design & conduct an epidemiological study					
Conduct a targeted literature review					
Communication to a non-scientific audience					
Publication in a peer-reviewed journal			*		
Oral presentation at a scientific conference					

\* A manuscript based on this project has been submitted for review to the peer-reviewed journal *Sexual Health*.

## Additional Applied Epidemiology Activities

During the MAE program I had the opportunity to be involved in a range of activities outside those required meet the core competencies of the program. Some of these activities included:

- For the second quarter of 2018 I coordinated Victorian HIV surveillance data at the Burnet Institute on behalf of DHHS, including data analysis for and production of the quarterly Victorian HIV surveillance report, and the reporting of jurisdictional surveillance data to the Kirby Institute for inclusion in national HIV surveillance and reporting.
- During 2019 I contributed to the management and analysis of gonorrhoea and chlamydia data extracted from the Burnet Institute's sentinel surveillance system, to produce the *2019 Victorian ACCESS Report*. This report is provided by the Burnet Institute to the Victorian Department of Health and Human Services on an annual basis.
- Throughout 2018-2019 I was involved in the surveillance of notifiable mycobacterial diseases (tuberculosis, Buruli ulcer and leprosy) at DHHS. This involved reviewing notifications of these diseases to assign them for follow-up by Public Health Officers or the Victorian Tuberculosis Program as required. I also presented a mycobacterial diseases surveillance report at the weekly CDES surveillance meeting.
- As part of the third MAE courseblock in early 2019 I was invited to present a lecture to my fellow MAE scholars on the basics of social network analysis. This additional teaching activity is presented as part of Appendix B. I was also invited by Deakin University to be a panel member for "Careers in Epidemiology and Environmental Health" at a careers workshop for final-year undergraduate biomedical science students.
- In June 2019 I travelled to Samoa as part of the SaMELFS Samoa study, where I worked as a team leader/epidemiologist for an entomology/molecular xenomonitoring survey. My duties as part of this study included:
  - Managing a field team consisting of two Australian entomologists and three Samoa Red Cross workers.
  - Managing and reconciling project fieldwork budgets, organising village visits, mosquito trap deployment and collection, and other logistical considerations and challenges associated with operating a project in a field setting.
  - Coordinating the collection, management and reporting of survey data using a cloud-based electronic data system and RStudio scripts.

My involvement in this study is further detailed in Appendix C.

## Chapter III

### Delays in Patient Presentation and Diagnosis for Buruli Ulcer (*Mycobacterium ulcerans* Infection) in Victoria, Australia, 2011–2017

#### Abstract

Uncertainty regarding transmission pathways and control measures makes prompt presentation and diagnosis for Buruli ulcer critical. To examine presentation and diagnosis delays in Victoria, Australia, we conducted a retrospective study of 703 cases notified between 2011 and 2017, classified as residing in an endemic (Mornington Peninsula; Bellarine Peninsula; South-east Bayside and Frankston) or non-endemic areas. Overall median presentation delay was 30 days (IQR 14–60 days), with no significant change over the study period ( $P=0.11$ ). There were significant differences in median presentation delay between areas of residence ( $P=0.02$ ), but no significant change over the study period within any area. Overall median diagnosis delay was 10 days (IQR 0–40 days), with no significant change over the study period ( $P=0.13$ ). There were significant differences in median diagnosis delay between areas ( $P<0.001$ ), but a significant decrease over time only on the Mornington Peninsula ( $P<0.001$ ). On multivariable analysis, being aged  $<15$  or  $>65$  years; having non-ulcerative disease; and residing in the Bellarine Peninsula or South-East Bayside (compared to non-endemic areas) were significantly associated with shorter presentation delay. Residing in the Bellarine or Mornington Peninsula and being notified later in the study period were significantly associated with shorter diagnosis delay. To reduce presentation and diagnosis delays, awareness of Buruli ulcer must be raised with the public and medical professionals, particularly those based outside established endemic areas.

## Background

The concept for this project originated before I started the MAE program, through my involvement with Buruli ulcer surveillance as a Public Health Officer in the Victorian Department of Health and Human Services' Communicable Disease Investigation and Response unit. Commencing the MAE allowed me access to the time and surveillance data needed to thoroughly examine delays in presentation and diagnosis for Buruli ulcer in Victoria.

To complete this project, I developed the methodology with the support of Ee Laine Tay, obtained ethics approval from the ANU HREC, completed data cleaning and analysis on the surveillance dataset, prepared the draft manuscript and coordinated the process of supervisor, co-author and peer review through to the final publication in *Tropical Medicine and Infectious Disease*, the official journal of the Australian College of Tropical Medicine.

## Lessons

This project was the first time that I had completed an application for ethics approval through a university human research ethics committee. Although this project was considered low risk, it underscored the importance of considering the ethical foundation of any epidemiological research using health data.

As my first significant experience with analysing rather than collecting surveillance data, I quickly learned that surveillance datasets are rarely complete or ready for analysis straight "out of the system". Missing or inconsistent historical data comes with the territory. This emphasised the importance of thorough, consistent data collection at all points of the surveillance process. The amount of an epidemiologist's time that goes into cleaning and preparing data before undertaking any analysis is something that many data consumers and end-users do not fully appreciate.

This project also served as a great learning opportunity to improve my skills with the Stata software package, which were at a functional but basic level at the start of the MAE. Likewise, the survival analysis methodology used to examine delays in presentation and diagnosis was new to me and allowed me to deepen my understanding of both the statistical tests involved in conducting a survival analysis, and how to organise data and perform these tests using Stata.

## Impact

The results of this project can be used by DHHS to target public health messaging regarding Buruli ulcer to medical practitioners in areas where lengthy delays in diagnosis remain. I hope

the findings regarding the lack of a decrease in presentation delays across the state will prompt a review of how the department communicates the risk of Buruli ulcer to the general public, and the importance of prompt presentation and diagnosis to minimise the severity and impact of the disease.

This study was published in the peer-reviewed journal *Tropical Medicine and Infectious Disease* in July 2019 – the final published manuscript forms the main body of this chapter. I also presented the results of the study at the ANU National Centre for Epidemiology and Population Health Seminar Series in February 2019. The slides for this presentation are included at the end of this chapter.

## Acknowledgements

I would like to acknowledge my co-authors on this project and the resulting paper – Ee Laine Tay, Colleen Lau, Emma Field and Michael Loftus. Their experience, expertise, advice and support were invaluable in making this project a success, and the first of my MAE projects to be completed and published in a peer-reviewed journal.

I would also like to acknowledge all those involved in the surveillance of Buruli ulcer in Victoria:

- Public Health Officers at the Victorian Department of Health and Human Services who follow-up notified cases (and chase outstanding notification details with doctors!) to ensure we have the best possible surveillance data to work with.
- The staff at the Mycobacteria Reference Laboratory at VIDRL for their work in confirming Buruli ulcer cases in the laboratory.
- Notifying medical practitioners, who provide the raw surveillance data on their patients.
- Finally, the Buruli ulcer patients themselves, who each have a unique experience and story to tell of their encounter with *Mycobacterium ulcerans* – thank you for taking the time to talk with us and share the details of your diagnosis and treatment to deepen our understanding of this fascinating neglected tropical disease.





Article

# Delays in Patient Presentation and Diagnosis for Buruli Ulcer (*Mycobacterium ulcerans* Infection) in Victoria, Australia, 2011–2017

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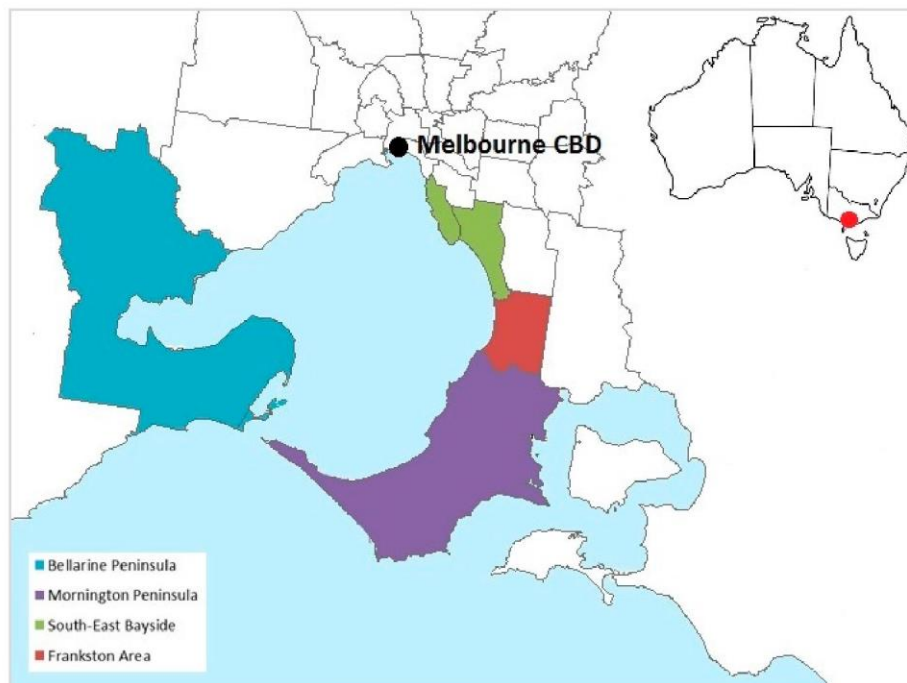
**Abstract:** Uncertainty regarding transmission pathways and control measures makes prompt presentation and diagnosis for Buruli ulcer critical. To examine presentation and diagnosis delays in Victoria, Australia, we conducted a retrospective study of 703 cases notified between 2011 and 2017, classified as residing in an endemic (Mornington Peninsula; Bellarine Peninsula; South-east Bayside and Frankston) or non-endemic area. Overall median presentation delay was 30 days (IQR 14–60 days), with no significant change over the study period ( $p = 0.11$ ). There were significant differences in median presentation delay between areas of residence ( $p = 0.02$ ), but no significant change over the study period within any area. Overall median diagnosis delay was 10 days (IQR 0–40 days), with no significant change over the study period ( $p = 0.13$ ). There were significant differences in median diagnosis delay between areas ( $p < 0.001$ ), but a significant decrease over time only on the Mornington Peninsula ( $p < 0.001$ ). On multivariable analysis, being aged  $<15$  or  $>65$  years; having non-ulcerative disease; and residing in the Bellarine Peninsula or South-East Bayside (compared to non-endemic areas) were significantly associated with shorter presentation delay. Residing in the Bellarine or Mornington Peninsula and being notified later in the study period were significantly associated with shorter diagnosis delay. To reduce presentation and diagnosis delays, awareness of Buruli ulcer must be raised with the public and medical professionals, particularly those based outside established endemic areas.

**Keywords:** Buruli ulcer; Australia; epidemiology; *Mycobacterium ulcerans*; skin ulcer; Tuberculosis and other mycobacteria

## 1. Introduction

Buruli ulcer is a destructive bacterial infection of skin and soft tissue caused by the toxin-producing environmental pathogen *Mycobacterium ulcerans*, which is most prevalent in sub-Saharan Africa [1]. Buruli ulcer is also an escalating public health issue in the temperate Australian state of Victoria, with incidence increasing since 2012 to a record high of 340 cases in 2018 [2]. The majority of Victoria's 6.4 million population reside in the metropolitan area of the state capital, Melbourne. Cases occur in residents and visitors to low-lying coastal areas considered endemic for the disease (Figure 1), many of which receive large numbers of visitors from non-endemic regions during summer. There is a seasonal pattern to disease onset—most infections become clinically apparent in autumn and winter, reflecting likely acquisition during summer or autumn based on an incubation period of up to nine months (median 4.8 months) [3,4]. Since 2012, incidence has declined in the long-established Bellarine

Peninsula endemic area, but has increased rapidly on the Mornington Peninsula, and to a lesser extent in the South-East Bayside suburbs [3].



**Figure 1.** Geographic areas in the state of Victoria, Australia, classified as endemic for Buruli ulcer for the purposes of the study, based on local government area boundaries. Non-shaded areas and areas not pictured were considered non-endemic. Inset shows the location of Melbourne, Victoria, within Australia.

Uncertainties about the exact mode of transmission, environmental reservoirs and drivers of emergence have hampered the design and implementation of effective interventions to reduce disease transmission. However, basic preventative measures such as avoiding mosquito bites and skin abrasions have been promoted by health authorities [5].

Buruli ulcer may manifest as an ulcer, papule, subcutaneous nodule or raised plaque. If untreated, it can progress to significant ulceration, tissue loss and bone involvement, resulting in permanent disfigurement and long-term morbidity [1]. Less commonly, the disease may present as an oedematous lesion, often characterised by an intact dermis with cellulitis and low-grade fever. This form of the disease can be rapidly progressive and lead to extensive tissue loss. Oedematous lesions may be misdiagnosed as cellulitis, leading to delays in the diagnosis and treatment [6]. Combination oral antibiotic therapy (rifampicin with clarithromycin or a fluoroquinolone) for a minimum of eight weeks is the first-line treatment for uncomplicated Buruli ulcer in Victoria [7]. Successful antibiotic treatment is often followed by prolonged wound healing time; a recent study in Victoria described a median of 138 days (interquartile range (IQR) 91–175 days) [8].

Given the current lack of effective interventions to reduce transmission, prompt diagnosis and treatment remain paramount. Delays in seeking medical care, confirming diagnosis, and commencing treatment can contribute significantly to morbidity through extended treatment and healing times, long-term disfigurement, and increased treatment costs [6,9,10]. Since a 2007 study focused on cases on the Bellarine Peninsula between 1998 and 2006 [11], there has been little research on factors influencing presentation and diagnosis delays in Victoria. Using routine surveillance data, this study aimed to characterise presentation and diagnosis delays for Buruli ulcer cases notified to the Victorian Department of Health and Human Services (DHHS) between 2011 and 2017, and identify factors influencing these delays.



## 2. Materials and Methods

### 2.1. Study Population

Buruli ulcer is a notifiable condition in Victoria, with mandatory reporting by clinicians and laboratories to DHHS. The initial study population included all laboratory-confirmed cases in Victorian residents diagnosed in Victoria and notified to DHHS from 2011 to 2017. If case presentation or diagnosis delay could not be ascertained due to missing data, they were excluded from the final study population.

### 2.2. Data Sources

Since 2011, Buruli ulcer case surveillance data were collected by the Victorian DHHS from medical practitioners using a standard surveillance form that includes demographic, clinical, treatment and risk history information. Data relevant to presentation and diagnosis delays are the date of first health care presentation, date of symptom onset, duration of symptoms before seeking care, and date on which Buruli ulcer was first clinically suspected. Many cases were initially diagnosed by a primary care doctor before referral to an infectious diseases specialist, meaning that the surveillance form may be completed by more than one medical practitioner. DHHS staff endeavour to contact all cases without a known link to a recognised endemic area by telephone for a detailed interview using a standard questionnaire. Data collected on enhanced surveillance forms and questionnaires were recorded in an electronic database.

### 2.3. Definitions

A confirmed case of Buruli ulcer required definitive laboratory evidence of infection, defined as the detection and specific identification of *Mycobacterium ulcerans* by culture on a specimen of tissue or a swab from a lesion (by the Mycobacterium Reference Laboratory at the Victorian Infectious Diseases Reference Laboratory) or the detection of the IS2404 insertion sequence by polymerase chain reaction.

Residential location was defined as the geographic area where the case was living at the time of notification. Geographic areas of residence were categorised into four areas (based on local government area boundaries) considered endemic for Buruli ulcer in Victoria—Mornington Peninsula, Bellarine Peninsula, South-east Bayside and Frankston Area. All other areas of Victoria were categorised non-endemic.

Lesion severity was classified as per World Health Organization definitions [12]. Category I was defined as a single lesion <5 cm diameter; Category II a single lesion 5–15 cm diameter; Category III a single lesion >15 cm, multiple lesions, lesions at a critical site (e.g., the eye) or osteomyelitis.

Presentation delay was defined as days from symptom onset to first presentation to a medical practitioner. Diagnosis delay was defined as days from presentation to a medical practitioner to first clinical suspicion of Buruli ulcer.

### 2.4. Data Analysis

De-identified data were extracted into Microsoft Excel and imported into STATA 15.1 (College Station, TX, USA) for analyses.

Data were descriptively analysed to characterise the study population. Presentation and diagnosis delays were described using median, IQR and range. The significance of change over time in median presentation and diagnosis delays were assessed using Kruskal–Wallis tests.

Univariate Cox's proportional hazards regression was used to identify significant associations between each dependent variable (presentation delay, diagnosis delay) and independent variables (age group, gender, year of notification, residential location at the time of notification, manifestation, lesion location, WHO lesion category). As the time-dependent variables represent a positive outcome (presentation or diagnosis), a hazard ratio of >1 indicates an association with shorter delay. Significance was assessed by the likelihood ratio test, with all independent variables with a *P*-value of <0.25

on univariate analysis considered for inclusion in a full multivariate model. A backward stepwise regression procedure ( $p \leq 0.05$ ) was performed to refine and select the final variables for the main effects model. Proportionality assumptions were tested using Schoenfeld and scaled Schoenfeld residuals. The fit of the final model was evaluated using Cox–Snell residuals. Any presentation or diagnosis delays recorded as zero days in the dataset were re-coded as 0.01 days for this analysis.

### 2.5. Ethics

Human research ethics approval was granted by the Australian National University Human Research Ethics Committee on 17 July 2018 (2018/442).

## 3. Results

### 3.1. Characteristics of the Study Population

Between 2011 and 2017, 877 confirmed cases of Buruli ulcer were notified to DHHS, and 703 (80%) cases were included in the study. Excluded were 174 cases for which presentation or diagnosis delay could not be ascertained from surveillance data. Significant differences were noted between the included and excluded cases for the clinical variables of lesion location, manifestation and WHO lesion category, likely because these data were collected primarily via surveillance forms which were not consistently completed by clinicians. Residential location differed between the included and excluded cases, reflecting more intensive public health follow-up of cases notified outside recognised endemic areas. The characteristics of the total, excluded and included cases are described in Table 1.

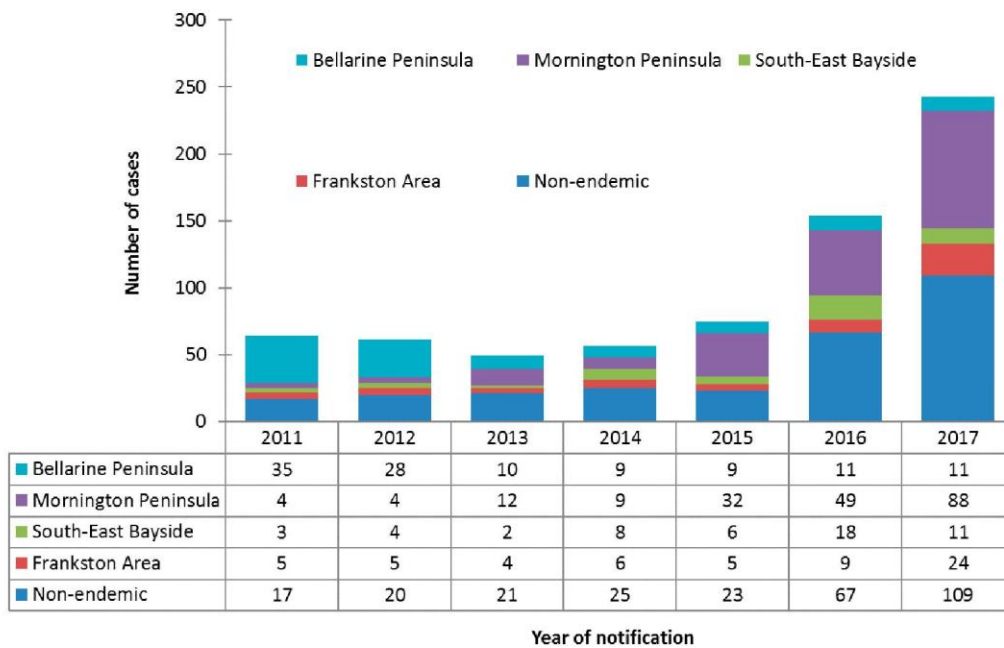
**Table 1.** Characteristics of Buruli ulcer cases (total, included and excluded for analysis) notified to the Victorian Department of Health and Human Services from 2011 to 2017.

	Total Notifications		Included for Analysis		Excluded for Analysis		P-Value
	no.	%	no.	%	no.	%	
<b>Sex</b>							0.15
Female	391	44.6	305	43.4	86	49.4	
Male	486	55.4	398	56.6	88	50.6	
<b>Age group</b>							0.95
<15 years	96	11.0	77	11.0	19	10.9	
15–65 years	495	56.4	395	56.2	100	57.5	
>65 years	286	32.6	231	32.9	55	31.6	
<b>Residential location</b>							<0.001
Bellarine Peninsula	184	21.0	113	16.1	71	40.8	
Mornington Peninsula	245	27.9	198	28.2	47	27.0	
South-East Bayside	63	7.2	52	7.4	11	6.3	
Frankston Area	75	8.6	58	8.3	17	9.8	
Non-endemic	310	35.4	282	40.1	28	16.1	
<b>Lesion location</b>							<0.001
Upper Limb	199	22.7	167	23.8	32	18.4	
Lower Limb	515	58.7	425	60.5	90	51.7	
Other *	104	11.9	91	12.9	13	7.5	
Unknown	59	6.7	20	2.8	39	22.4	
<b>Manifestation</b>							<0.001
Ulcer	644	73.4	549	78.1	95	54.6	
Non-ulcer †	154	17.6	138	19.6	16	9.2	
Unknown	79	9.0	16	2.3	63	36.2	
<b>WHO lesion category</b>							<0.001
I	619	70.6	539	76.7	80	46.0	
II	110	12.5	91	12.9	29	10.9	
III	60	6.8	55	7.8	5	2.9	
Unknown	88	10.0	18	2.6	70	40.2	

\* includes lesions on areas of the body other than limbs, and lesions in multiple locations (including limbs). † includes all non-ulcerative Buruli ulcer manifestations.



Incidence increased over the study period in all areas except the Bellarine Peninsula, where incidence decreased from 35 cases in 2011 to 11 cases in 2017. The greatest increase in incidence was observed for cases on the Mornington Peninsula, from four cases in 2011 to 88 cases in 2017. Cases residing in non-endemic areas also increased significantly over the study period, from 17 cases in 2011 to 109 cases in 2017. The number and proportionate distribution of cases over the study period by area of residence is summarized in Figure 2.



**Figure 2.** Counts and proportionate distributions of Buruli ulcer cases in the study population notified to the Department of Health and Human Services from 2011 to 2017, by area of residence ( $n = 703$ ).

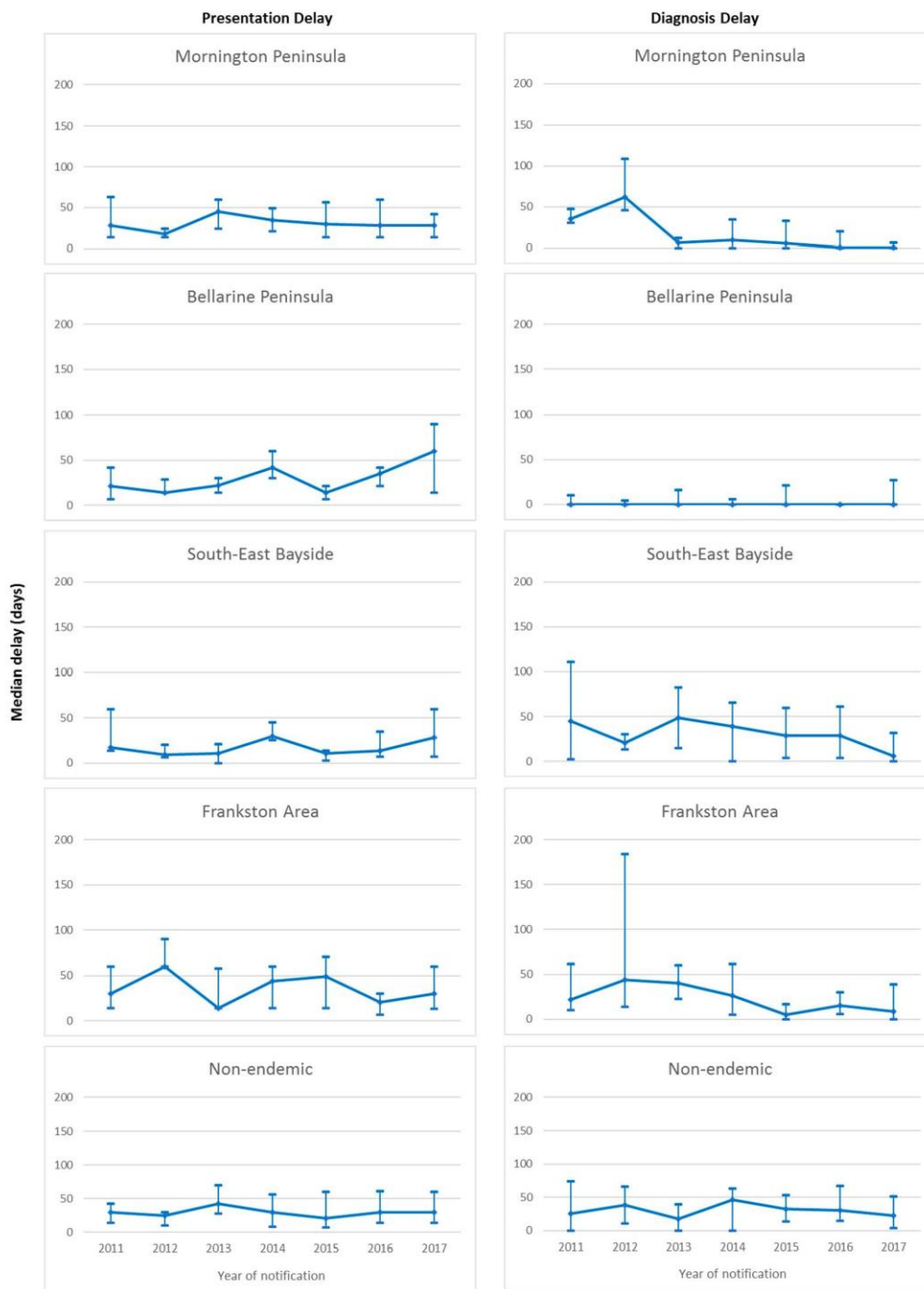
### 3.2. Presentation and Diagnosis Delays

#### 3.2.1. Presentation Delay

Overall median presentation delay was 30 days (IQR 14–60 days), with no significant change over the study period ( $p = 0.11$ ). Significant differences in median presentation delay between areas of residence were observed over the study period ( $p = 0.02$ ), with shortest delay in South-east Bayside (19 days, IQR 7–35.5 days), followed by the Bellarine Peninsula (21 days, IQR 14–42 days), Mornington Peninsula (29.5 days, IQR 14–56 days), and Frankston and non-endemic areas (both 30 days, IQR 14–60 days). No significant change in median presentation delay was observed within any of the areas of residence over the study period (Figure 3).

#### 3.2.2. Diagnosis Delay

Overall median diagnosis delay was 10 days (IQR 0–40 days), with no significant change observed over the study period ( $p = 0.13$ ). Significant differences in median diagnosis delay between areas of residence were observed ( $p < 0.001$ ). Median diagnosis delay was shortest on the Bellarine Peninsula (0 days, IQR 0–7 days) and the Mornington Peninsula (0 days, IQR 0–19 days), followed by Frankston (16 days, IQR 3–45 days), South-east Bayside (20.5 days, IQR 1–61 days) and non-endemic areas (29 days, IQR 7–56 days). Significant decrease in median diagnosis delay over the study period was observed only for the Mornington Peninsula ( $p < 0.001$ ), however the median remained at zero days for all years of the study period on the Bellarine Peninsula. Non-significant decreases were observed in South-East Bayside and Frankston. No decrease was observed for the non-endemic areas. Median diagnosis delay over the study period by area of residence is illustrated in Figure 3.



**Figure 3.** Median and interquartile ranges for presentation and diagnosis delays (days) of Buruli ulcer cases in the study population notified to the Victorian Department of Health and Human Services from 2011 to 2017, by area of residence.

### 3.3. Factors Influencing Presentation and Diagnostic Delays

#### 3.3.1. Presentation Delay

Table 2 provides a summary of associations between independent variables and presentation delay on univariate and multivariate Cox regression analysis. In the final multivariate model, being aged <15 years or >65 years, having non-ulcerative disease, and residing in the Bellarine Peninsula or South-East Bayside compared to a non-endemic area remained significantly associated with shorter presentation delay.

**Table 2.** Associations between independent variables and presentation delay on univariate and multivariate Cox's regression analysis.

	Observations	Median Delay (days)	Univariate			Multivariate		
			Crude HR	95% CI	P-Value	Adjusted HR	95% CI	P-Value
<b>Sex</b>								
Female	305	28	1.06	0.91–1.23	0.47			
Male	398	30	Reference					
<b>Age group</b>								
<15 years	77	21	<b>1.31</b>	<b>1.02–1.67</b>	<b>0.03</b>	<b>1.35</b>	<b>1.04–1.73</b>	<b>0.02</b>
15–65 years	395	30	Reference			Reference		
>65 years	231	23	<b>1.29</b>	<b>1.09–1.52</b>	<b>0.002</b>	<b>1.31</b>	<b>1.10–1.55</b>	<b>0.002</b>
<b>Residential location</b>								
Bellarine Peninsula	113	21	<b>1.20</b>	<b>0.97–1.50</b>	<b>0.10</b>	<b>1.26</b>	<b>1.01–1.58</b>	<b>0.04</b>
Mornington Peninsula	198	29.5	1.07	0.89–1.28	0.48	1.06	0.88–1.28	0.53
South-East Bayside	52	19	<b>1.40</b>	<b>1.04–1.88</b>	<b>0.03</b>	<b>1.44</b>	<b>1.06–1.95</b>	<b>0.02</b>
Frankston area	58	30	0.88	0.66–1.17	0.38	0.87	0.65–1.17	0.36
Other (non-endemic)	282	30	Reference			Reference		
<b>Lesion location</b>								
Upper limb	167	30	Reference					
Lower limb	425	30	1.04	0.87–1.24	0.69			
Other *	91	21	1.16	0.89–1.49	0.27			
<b>Manifestation</b>								
Ulcer	549	30	Reference			Reference		
Non-ulcer †	138	21	<b>1.28</b>	<b>1.06–1.54</b>	<b>0.01</b>	<b>1.27</b>	<b>1.05–1.53</b>	<b>0.02</b>
<b>Year of notification</b>								
Increasing from 2011	703	-	<b>0.97</b>	<b>0.93–1.00</b>	<b>0.06</b>			
<b>WHO lesion category</b>								
I	539	30	1.07	0.85–1.33	0.57			
II	91	28	Reference					
III	55	28	<b>1.30</b>	<b>0.93–1.81</b>	<b>0.13</b>			

\* includes lesions on areas of the body other than limbs, and lesions in multiple locations (including limbs). † includes all non-ulcerative Buruli ulcer manifestations. HR = hazard rate CI = confidence interval. **Bold type** indicates significance for inclusion in the full and main effects models.

### 3.3.2. Diagnosis Delay

Table 3 provides a summary of associations between independent variables and diagnosis delay on univariate and multivariate Cox regression analysis. In the final multivariate model, residing in the Bellarine Peninsula or Mornington Peninsula compared to a non-endemic area and being notified later in the study period remained significantly associated with shorter diagnosis delay.

**Table 3.** Associations between independent variables and diagnosis delay on univariate and multivariate Cox's regression analysis.

	Observations	Median Delay (days)	Univariate			Multivariate		
			Crude HR	95% CI	P-Value	Adjusted HR	95% CI	P-Value
<b>Sex</b>								
Female	305	14	<b>0.89</b>	<b>0.77–1.04</b>	<b>0.14</b>			
Male	398	7	Reference					
<b>Age group</b>								
<15 years	77	19	<b>0.84</b>	<b>0.66–1.08</b>	<b>0.17</b>			
15–65 years	395	13	Reference					
>65 years	231	7	1.08	0.92–1.28	0.33			
<b>Residential location</b>								
Bellarine Peninsula	113	0	<b>2.63</b>	<b>2.09–3.30</b>	<b>&lt;0.001</b>	<b>3.18</b>	<b>2.47–4.09</b>	<b>&lt;0.001</b>
Mornington Peninsula	198	0	<b>1.97</b>	<b>1.63–2.37</b>	<b>&lt;0.001</b>	<b>1.94</b>	<b>1.60–2.35</b>	<b>&lt;0.001</b>
South-East Bayside	52	20.5	1.04	0.77–1.39	0.82	1.07	0.79–1.44	0.67
Frankston area	58	16	1.17	0.88–1.55	0.28	1.21	0.91–1.61	0.19
Other (non-endemic)	282	29	Reference			Reference		
<b>Lesion location</b>								
Upper limb	167	12	Reference					
Lower limb	425	13	1.02	0.85–1.22	0.823			
Other *	91	6	1.14	0.88–1.47	0.32			



Table 3. Cont.

	Observations	Median Delay (days)	Univariate			Multivariate		
			Crude HR	95% CI	P-Value	Adjusted HR	95% CI	P-Value
<b>Manifestation</b>								
Ulcer	549	10	Reference					
Non-ulcer †	138	13.5	0.95	0.79–1.15	0.60			
<b>Year of notification</b>								
Increasing from 2011	703	-	<b>1.03</b>	<b>0.99–1.06</b>	<b>0.19</b>	<b>1.09</b>	<b>1.04–1.13</b>	<b>&lt;0.001</b>
<b>WHO lesion category</b>								
I	539	9	<b>1.26</b>	<b>1.01–1.58</b>	<b>0.04</b>			
II	91	19	Reference					
III	55	31	0.87	0.62–1.22	0.41			

\* includes lesions on areas of the body other than limbs, and lesions in multiple locations (including limbs). † includes all non-ulcerative Buruli ulcer manifestations. HR = hazard rate CI = confidence interval. **Bold type** indicates significance for inclusion in the full and main effects models.

#### 4. Discussion

This study found that despite a significant difference in median presentation delay between areas of residence, presentation delay had not significantly decreased in Victoria as a whole, or in any specific area during the period 2011–2017. There was a significant association between shorter presentation delays and residence in South-East Bayside or Bellarine Peninsula. This is consistent with a recent study by Loftus et al. (using a similar surveillance dataset covering 2011–2016), which identified shortest presentation delays for cases with likely exposure to the disease on the Bellarine Peninsula compared to the rest of Victoria, however the difference was not considered significant [3]. Significant association between cases aged <15 years or >65 years and shorter presentation delays is also consistent with previous findings [3]. Significant association between shorter presentation delays and having non-ulcerative disease has been previously identified in a study in Benin [13].

There was no significant decrease in median diagnosis delay in Victoria as a whole, however a significant decrease was observed on the Mornington Peninsula even as case numbers increased year on year, reaching a zero-day median in 2016. There was a significant association between shorter diagnosis delays and residence in Bellarine or Mornington Peninsula, and with diagnosis later in the study period. These findings are consistent with previous studies in Victoria, which identified shortest diagnosis delays in established endemic areas [3,11,14]. A recent study using a similar surveillance dataset found that most cases in non-endemic areas had a likely exposure to one or more of the endemic areas during their plausible acquisition period [3].

The zero-day median diagnosis delay on the Bellarine Peninsula throughout the study period is likely reflective of its longer history as an endemic area and higher clinical index of suspicion among local medical practitioners. Likewise, the significant decrease on the Mornington Peninsula is likely related to growing medical practitioner and resident familiarity with the disease over the study period as case numbers increased locally and the disease received additional attention from public health authorities, the medical community and the media. The results of the multivariate analysis support this hypothesis, with residence in the two areas that have previously or are currently experiencing intense endemic transmission being associated with significantly shorter diagnosis delay. DHHS has made significant efforts to raise awareness of the disease as it has emerged in these areas, including advisory notices from the state's Chief Health Officer and an online continuing professional development module for primary care doctors [5,15].

The association between shorter presentation delays and cases being aged <15 years or >65 years may be due to an increased caution about health issues in children and older people. A previous Victorian study found that children and older people are at greater risk of severe Buruli ulcer disease [2]. The association between shorter presentation delays and non-ulcerative disease may be because these symptoms (i.e., oedema, cellulitis and plaques) are less likely to be dismissed as insect bites, are often rapidly progressive and can involve systemic symptoms like fever.



This study utilized a large, robust surveillance dataset and included 80% of cases notified in Victoria over the study period. Limitations included the retrospective nature of surveillance data, and exclusion of cases due to missing data, and the fact that the majority of cases resided in endemic areas, which may have biased the data. We were also unable to include other factors that may impact on presentation and diagnosis delays such as medical co-morbidities, occupation, social connectivity, socioeconomic status, educational level or geographic distance to health care facilities as these are not collected as part of routine surveillance. Place of residence was recorded only at the time of notification and may be different to when the disease was acquired or diagnosed, due to the potentially extended incubation period and delays in presentation and diagnosis.

On a global scale, delays in presentation and diagnosis for Buruli ulcer in Victoria are relatively short—a study of 82 Nigerian patients in Benin identified a median delay from symptom onset to diagnosis of 29 weeks (IQR 12–234) [16]. Lengthy delays have also been reported in Cameroon (median 12 weeks, IQR 3–30,  $n = 105$ ) and Nigeria (median 12 weeks, IQR 6–50,  $n = 145$ ) [17,18]. It is important to recognise the differing drivers for delays in each context—whilst geographical and economic inaccessibility to health care and an initial preference for traditional healing methods have been identified in Africa, [16,19] these are highly unlikely to be important factors in Victoria.

To further reduce delays in diagnosis, public health authorities must continue to find ways to engage with and effectively raise clinician awareness of Buruli ulcer, particularly those based outside the recognised endemic areas. Clinicians may be unfamiliar with or have a low level of clinical suspicion if patients acquired Buruli ulcer many months earlier while visiting an endemic area. This contention is supported by the relatively lengthy diagnosis delays observed for cases residing in non-endemic areas compared to those in recognised endemic areas, and the lack of an observable decrease in median diagnosis delay over the study period.

The absence of a decrease in presentation delay over the study period suggests that a review of public health communications and community engagement (including the importance of early presentation, early diagnosis and preventative measures) may be warranted. In a study of 85 patients in the Bellarine Peninsula, seeing media related to Buruli ulcer was a significant factor in seeking diagnosis for nearly one quarter of cases [11]. A review of communications and community engagement could gauge the effectiveness of current strategies for raising awareness among local communities and visitors to endemic areas and identify areas for improvement.

As Buruli ulcer incidence continues to increase in Victoria, effective interventions to reduce transmission are limited due to continuing uncertainty regarding the modes of transmission. Effective risk communication and awareness remain critical to reducing the disease burden.

**Author Contributions:** Conceptualization, S.C. and E.L.T.; methodology, S.C. and E.L.T.; formal analysis, S.C.; investigation, S.C.; data curation, S.C., E.L.T. and M.L.; writing—original draft preparation, S.C.; writing—review and editing, S.C., C.L., E.F., M.L. and M.T.; visualization, S.C.; supervision, C.L., E.F. and E.L.T.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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# Oral Presentation at the ANU National Centre for Epidemiology and Population Health Seminar Series – Canberra, Australia

27 February 2019

Australian National University  
VICTORIA Health and Human Services

## A Neglected Tropical Disease in the Temperate Zone: Buruli Ulcer in Victoria

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Australian National University  
VICTORIA Health and Human Services


### What is Buruli ulcer?

Destructive disease of skin and soft tissue.

Caused by the environmental bacteria *Mycobacterium ulcerans*.

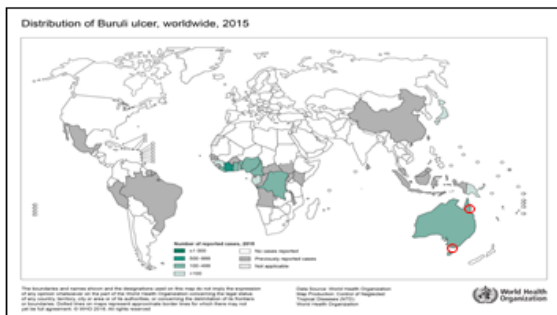
Diagnosis rapidly confirmed by PCR.

Combination oral antibiotic therapy for 8 weeks - frontline treatment in Australia.



Severe ulcerative Buruli ulcer lesion on the knee of an 11 year old boy. Jones, Paul, Daniel O'Brien et al. 2018

Culture presentation of Buruli Ulcer on the leg of a 17 year old man. Donnelly, Paul, Paul Jarman et al. 2018



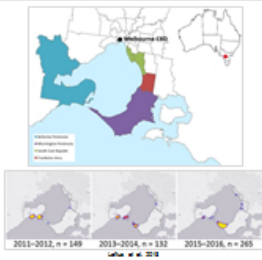
Australian National University  
VICTORIA Health and Human Services

### Buruli ulcer in Victoria

Highly focal spatial distribution.

Increasing cases, shifting spatial epidemiology.

Mode(s) of transmission, reservoir(s) and drivers for emergence remain unclear.



2011-2012, n = 149  
2013-2014, n = 332  
2015-2016, n = 285  
Jellum et al. 2018



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### The environment

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### The human population

8

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### The vector?

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### The reservoirs?

Common brushtail possum  
*Trichurus vulpecula*

Common ringtail possum  
*Pseudocheirus peregrinus*

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### Possible transmission pathways

Small mammals: e.g. possums

Humans

Environment: e.g. plants, animal faeces, stagnant water, drains, ...

Insect vector: e.g. mosquitoes

1- ecosystem changes

Proposed transmission pathways for D. viverrina  
Lester, van Dyk, et al. 2010



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### Current public health advice



- Wear gardening gloves, long-sleeved shirts and trousers when working outdoors.
- Avoid insect bites by using suitable insect repellents.
- Protect cuts or abrasions with sticking plasters.
- Promptly wash and cover any scratches or cuts received while working outdoors.
- See a doctor if you have a slow-healing skin lesion.

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In the absence of proven effective control measures, prompt presentation, diagnosis and treatment is critical to reduce the disease burden in Victoria...

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### Delays in patient presentation and diagnosis for Buruli ulcer in Victoria, 2011-2017

Aims:

- To characterise presentation and diagnosis delays for Buruli ulcer cases notified in Victoria between 2011 - 2017.
- To identify factors influencing these delays.

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### Data sources



*Mycobacterium ulcerans* infection has been notifiable since 2004.

Surveillance data collected from diagnosing and treating medical practitioners.

Systematic surveillance data collection since 2011.




15






### Definitions

**Buruli ulcer case** – *M. ulcerans* detected on PCR or culture from a clinical specimen.



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### Study population



877 cases notified during the study period.

74 cases excluded due to missing date data.

703 cases included (80% of total notifications).

	Total notifications		Included		Excluded	
	n	%	n	%	n	%
Sex						
Male	392	44.6	352	40.1	40	4.6
Female	485	55.4	351	40.1	134	15.4
Age group						
0-10 years	92	10.5	77	8.9	15	1.7
11-19 years	49	5.6	39	4.5	10	1.1
20-29 years	286	32.6	232	26.8	54	6.2
30-39 years	249	28.3	199	22.8	50	5.7
40-49 years	141	16.1	109	12.5	32	3.7
50-59 years	61	7.0	49	5.6	12	1.4
60-69 years	41	4.7	34	3.9	7	0.8
70-79 years	33	3.8	26	3.0	7	0.8
80-89 years	19	2.2	15	1.7	4	0.5
90-99 years	10	1.1	7	0.8	3	0.3
Unknown	10	1.1	10	1.1	0	0.0
Residence						
Greater Geelong	108	12.3	87	10.0	21	2.4
Greater Melbourne	516	58.9	419	48.1	97	11.1
Other	153	17.4	97	11.2	56	6.4
Unknown	59	6.7	20	2.3	39	4.5
Manifestation						
Other	109	12.5	109	12.5	0	0.0
Non-ULC	109	12.5	109	12.5	0	0.0
Unknown	769	87.5	585	66.9	184	21.1
WHO ulcer category						
U	129	14.7	91	10.5	38	4.3
UL	489	55.8	389	44.7	100	11.5
Unknown	89	10.1	18	2.1	71	8.2

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### Methods

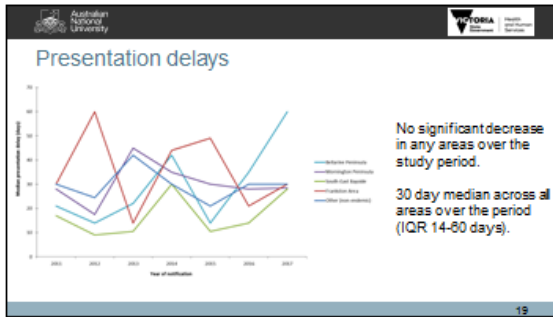
Univariate Cox's proportional hazards regression model.



Identify significant associations between:

- Time-based dependent variables (presentation delay and diagnosis delay in days)
- Independent variables (sex, age, residence, lesion location, manifestation, WHO category)

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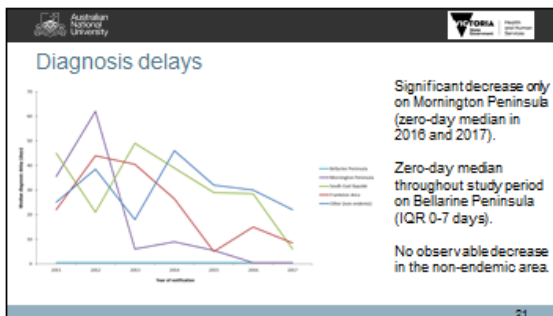





### Factors influencing presentation delay

Significantly associated with shorter presentation delay:

- Being <15 years or >85 years of age.
- Having a non-ulcerative form of disease.
- Residing in the Bellarine Peninsula or South-East Bayside areas compared to a non-endemic area.

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### Factors influencing diagnosis delay

Significantly associated with shorter diagnosis delay:

- Residing in the Bellarine Peninsula or Mornington Peninsula areas compared to a non-endemic area.
- Being notified later in the study period.

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### Conclusions

Presentation delays have not significantly decreased across the state, even in well-established endemic areas:

- Community awareness?
- How effective is current public health messaging?

Diagnosis delays have decreased, but remain high in non-endemic areas:

- Most non-endemic cases have been exposed in an endemic area.
- Low level of clinical suspicion outside endemic areas?
- Greater GP education / awareness needed.

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### Ongoing research into Buruli ulcer

NHMRC partnership project "Beating Buruli in Victoria"

Department of Health and Human Services  
 Barwon Health  
 Mornington Peninsula Shire  
 Austin Health  
 CSIRO  
 AgriBio  
 University of Melbourne



<http://www2.health.vic.gov.au/public-health/for-you/diseases/buruli-ulcer/>

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Australian National University

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Dr Michael Loftus (Alfred Health)

DHHS Public Health Officers

Mycobacteria Reference Laboratory at VIDRL

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25

Australian National University

QUESTIONS?



Chalvey Beach, Point Nepean National Park

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## Chapter IV

### The epidemiology and subtype diversity of HIV-1 in the newly-arrived Asian-born MSM population in Victoria, Australia 2015-2018: An observational study based on routinely collected surveillance data

#### Abstract

We used routinely collected surveillance data to improve our understanding of locally-acquired HIV transmission and sexual mixing within and between the newly-arrived Asian-born and Australian-born men who have sex with men (MSM) populations.

The study population included 444 newly-diagnosed HIV cases notified between 1 January 2015 – 31 December 2018 with subtyping data available. 84% were classified as locally-acquired and 16% as overseas-acquired.

Epidemiological data collected from diagnosing medical practitioners were linked to subtyping data from the state reference laboratory. Populations were characterised using frequencies, percentages, medians and interquartile ranges. Comparisons between populations were made using the chi-squared, Fisher's exact, or Mann-Whitney U test. Exact binomial confidence intervals were calculated for proportions.

Of the locally-acquired cases, were 267 Australian-born and 104 newly-arrived Asian born. Thirteen HIV-1 forms were observed including four pure subtypes (n=271, 73%), five circulating (n=94, 25%) and four unique recombinant forms (n=6, 2%). Most infections were subtype B (212/267, 79%) in Australian-born and non-B (62/104, 60%) in newly-arrived Asian-born MSM. Newly-arrived Asian-born cases were younger (median age 29 vs 32 years,  $P=0.02$ ) and had a lower median CD4+ cell count at diagnosis (365 vs 449 cells/ $\mu$ L,  $P=0.009$ ). In Asian-born cases, subtype B accounted for a larger proportion of locally-acquired infections compared to the overseas-acquired infections (40% vs 29%,  $p=0.21$ )

These findings provide important biological data to support the theory that local transmission in both populations is mostly assortative based on ethnicity. However, the 40% of Asian-born MSM infected with subtype B and 21% of Australian-born with non-B subtypes may be suggestive of sexual mixing and local transmission between the two populations. We must better understand the prevention, testing and treatment needs of the growing newly-arrived Asian-born MSM population and address them in a culturally appropriate manner.



## Background

The concept for this project was originally conceived by Professor Margaret Hellard at the Burnet Institute. We had initially hoped to use HIV-1 whole genome sequencing data to identify transmission clusters and examine transmission within and between the Australian-born and newly-arrived Asian-born MSM populations. However, due to constraints at the public health laboratory over the period in which I needed to complete the project, we were unable to do so. We therefore made the decision to continue with the project using readily available and routinely collected subtyping and epidemiological surveillance data.

To complete this project, I developed the project proposal and data analysis plan, obtained ethics approval from the ANU HREC, submitted a data request to DHHS to obtain the linked surveillance and subtyping data, cleaned and analysed the data, interpreted and presented the results of analyses and prepared the manuscript.

Feedback and guidance were provided by my placement and academic supervisors (particularly Carol El-Hayek) throughout the project, as well as from other co-authors on the manuscript developed for publication.

## Lessons

This study once again underscored the importance of good data collection processes at all points in a passive surveillance system; from the notifying doctor, the public health officer, the epidemiologist and the design of the surveillance system itself. Missing or inconsistent data fields (e.g. place of birth, year of arrival in Australia or exposure risk) that could have been easily rectified at the time of notification can mean the exclusion of many cases from a retrospective study.

It also served to illustrate, despite the above-mentioned limitations, how routinely collected epidemiological and laboratory surveillance data can be retrospectively analysed together to characterise emerging at-risk populations and provide a starting point and impetus for further research.

Finally, I came to appreciate the benefits of whole genome sequencing over subtyping for exploring and inferring HIV transmission clusters. The superior resolution provided by whole genome sequencing could provide a far more detailed picture of HIV transmission within and between risk populations, allowing for a more thorough exploration of transmission patterns and the targeting of interventions. I have no doubt that this research will be done to further characterise HIV transmission in at-risk population in Victoria in the coming years.

## Impact

Understanding and addressing HIV transmission in the newly-arrived Asian-born MSM population is increasingly important in Victoria, with both the population and the proportion of HIV notifications from the population increasing in recent years. I hope that this study, along with those cited in the chapter, provides an impetus for further research, evidence-based public health policy and effective services and interventions to reduce the incidence of HIV in this population.

The results of this study were presented as an invited oral presentation at the International Union Against Sexual Transmitted Infections (IUSTI) Asia-Pacific Conference in Shanghai, China in October 2019. The slides for this presentation are included at the end of the chapter.

A manuscript based on this project has been submitted for review to the peer-reviewed journal *Sexual Health*. Published by the CSIRO, *Sexual Health* is the official journal of the IUSTI Asia-Pacific region.

## Acknowledgements

I would like to acknowledge the following individuals for their assistance on this study:

- Carol El-Hayek at the Burnet Institute for her valuable and challenging input into the study and resulting manuscript.
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- Nasra Higgins and Shakti Gounder the Victorian Department of Health and Human Services for processing my data request and providing feedback on the manuscript.

# The epidemiology and subtype diversity of HIV-1 in the newly-arrived Asian-born MSM population in Victoria, Australia 2015-2018: An observational study based on routinely collected surveillance data

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## Abstract

### Background

We used routinely collected surveillance data to improve our understanding of locally-acquired HIV transmission and sexual mixing within and between the newly-arrived Asian-born and Australian-born men who have sex with men (MSM) populations.

### Methods

The study population included 444 newly-diagnosed HIV cases notified between 1 January 2015 – 31 December 2018 with subtyping data available. 84% were classified as locally-acquired and 16% as overseas-acquired.

Epidemiological data collected from diagnosing medical practitioners were linked to subtyping data from the state reference laboratory. Populations were characterised using frequencies, percentages, medians and interquartile ranges. Comparisons between populations were made using the chi-squared, Fisher's exact, or Mann-Whitney U test. Exact binomial confidence intervals were calculated for proportions.

### Results

Of the locally-acquired cases, were 267 Australian-born and 104 newly-arrived Asian born. Thirteen HIV-1 forms were observed including four pure subtypes (n=271, 73%), five circulating (n=94, 25%) and four unique recombinant forms (n=6, 2%). Most infections were subtype B (212/267, 79%) in Australian-born and non-B (62/104, 60%) in newly-arrived Asian-born MSM. Newly-arrived Asian-born cases were younger (median age 29 vs 32 years,  $P=0.02$ ) and had a lower median CD4+ cell count at diagnosis (365 vs 449 cells/ $\mu$ L,  $P=0.009$ ). In Asian-born cases, subtype B accounted for a larger proportion of locally-acquired infections compared to the overseas-acquired infections (40% vs 29%,  $p=0.21$ )

## Discussion

These findings provide important biological data to support the theory that local transmission in both populations is mostly assortative based on ethnicity. However, the 40% of Asian-born MSM infected with subtype B and 21% of Australian-born with non-B subtypes may be suggestive of sexual mixing and local transmission between the two populations. We must better understand the prevention, testing and treatment needs of the growing newly-arrived Asian-born MSM population and address them in a culturally appropriate manner.

## Background

In the state of Victoria, Australia the number of newly-diagnosed HIV cases notified to the Department of Health and Human Services (DHHS) among men who have sex with men (MSM) has decreased from 234 cases in 2016 to 155 in 2018.<sup>1</sup> This decline was likely a result of the increasingly widespread availability of HIV testing, pre-exposure prophylaxis (PrEP) and antiretroviral treatment as prevention, all of which are supported by state and national HIV strategies.<sup>2-4</sup> Recent surveillance and research attributes the majority of the decline to a reduction in diagnoses in Australian-born MSM. In contrast, the proportion of total incident cases from the newly-arrived Asian-born MSM population has been increasing.<sup>1, 5, 6</sup> One study based in Melbourne, Victoria found newly-arrived Asian-born MSM were more than four times more likely to be diagnosed with incident HIV than Australian-born MSM by the end of the five-year study period in 2017.<sup>6</sup> The comparatively young median age and newly-arrived status of Asian-born MSM in this study (26.4 years, interquartile range 23.5 - 29.8) suggests that the population may be primarily international students.

Victoria has a growing temporary resident population of international students originating from Asian nations. In 2018, over 200,000 international students enrolled in post-secondary educational institutions in Victoria; nine of the top ten countries of origin for these students were located in Asia.<sup>7</sup> Among newly-arrived Asian-born MSM, especially those on time-limited student visas, increasing HIV diagnoses may be due in part to: a lack of access to Australian government-funded medical (Medicare) and pharmaceutical (Pharmaceutical Benefits Scheme (PBS)) preventative health services such as HIV testing, pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART);<sup>8</sup> poorer knowledge of sexual health and risk reduction strategies;<sup>9</sup> stigmatisation and/or criminalisation of male-to-male sexual activity in their home country;<sup>10</sup> and lower levels of identification with and connection to the local gay community and culture.<sup>11</sup> Previous research, based on self-reported patient data, has suggested there may be significant assortative sexual mixing among Asian-born MSM in Victoria.<sup>6</sup> As a result of assortative sexual mixing by ethnicity, and the potentially higher prevalence of undiagnosed

and/or untreated HIV within this population, newly-arrived Asian-born MSM may also be at higher risk of sexual contact with a partner who is infectious for HIV.<sup>12</sup>

HIV subtyping data can provide an indication of the likely geographic origin of infections, and of transmission between populations.<sup>13</sup> The HIV-1 group M virus is responsible for the vast majority of HIV infections worldwide.<sup>14</sup> It is currently classified into nine subtypes (A–D, F–H, J and K), six sub-subtypes (A1–A4, F1 and F2) and an increasing number of circulating and unique recombinant forms (CRFs and URFs). This subtype diversity has primarily evolved due to the rapid generation and reverse transcriptase error rate of the virus.<sup>15</sup> Recombinant forms can arise when multiple viruses of differing subtypes infecting an individual simultaneously recombine – they may later be recognised as CRFs based on ongoing transmission.<sup>16</sup> The clinical significance of these different subtypes remains unclear, though there is some evidence that disease progression and CD4 count recovery after the commencement of treatment may differ between subtypes.<sup>17,18</sup> As HIV-1 has spread globally, differences in epidemic timing and population characteristics, structure and movements have resulted in the divergence of subtype diversity and predominant subtypes between geographical areas.<sup>19</sup> Previous research indicates the majority of incident HIV cases in the Australian-born MSM population are of the HIV-1 B subtype, which is also predominant throughout North America and Europe.<sup>20,21</sup> With the exception of Japan and South Korea,<sup>22,23</sup> non-B subtypes and CRFs predominate throughout Asia, with the diversity and predominant strains varying country-to-country.<sup>24</sup>

It could be expected that if there was sexual mixing and local transmission between the newly-arrived Asian-born MSM (from countries where non-B subtypes predominate) and Australian-born MSM populations (where subtype B predominates), a significant proportion of infections in newly-arrived Asian-born MSM would be subtype B, and a significant proportion of infections in Australian-born MSM would be non-B subtypes.

we combined routinely collected epidemiological and genotyping surveillance data to improve our understanding of locally-acquired HIV transmission and sexual mixing within and between the newly-arrived Asian-born and Australian-born MSM populations.

## Methods

### Data sources

The Victorian Department of Health and Human Services (DHHS) routinely collects HIV surveillance data from diagnosing medical practitioners through a statutory notification process.<sup>25</sup> Surveillance data are submitted by medical practitioners to DHHS using a standardised HIV notification form and recorded electronically on the Public Health Event Surveillance System (PHESS) database. The enhanced surveillance form collects data on case

demographics, clinical characteristics and HIV testing, risk and exposure history. These data are generally based on self-reported information provided to the clinician by the case. Data completeness for the surveillance forms varies, however DHHS public health officers undertake follow-up with notifying medical practitioners if key data fields are not completed.

Partial sequencing of the HIV *pol* gene and subtyping analysis was performed at the Victorian Infectious Diseases Reference Laboratory (VIDRL). Sequencing is done at the request of the treating medical practitioner, resulting in subtyping data being available for only a subset of notified cases in Victoria during the study period. In collaboration with VIDRL, subtyping data for each case are matched to the DHHS routinely-collected HIV surveillance data using a unique identification number generated in PHESS. For cases with multiple sequences in the subtyping dataset (primarily due to repeated testing for drug resistance purposes), the earliest available sequence was used for this study.

### Definitions

The following definitions were used to define the study population, based on risk and exposure data fields routinely collected by DHHS for HIV surveillance.

- Australian-born – country of birth recorded as Australia.
- Asian-born – country of birth recorded as one of the 53 sovereign states in Asia.
- Locally-acquired – likely place of acquisition recorded as Australia.
- Overseas-acquired – likely place of acquisition recorded as a country other than Australia.
- Newly-arrived – year of arrival in Australia recorded as  $\leq 4$  years before first recorded HIV diagnosis. This cut-off aimed to capture most Asian-born international students on time-limited student immigration visas (a key population of interest in this setting) whilst excluding individuals who have lived in-country for extended periods of time.
- MSM – at least one risk for exposure to HIV recorded as male-to-male sexual contact. Individuals who identified as transgender and reported sex with MSM were included.

### Study population

The study population included all newly-diagnosed HIV cases notified to DHHS during the study period (1 January 2015 – 31 December 2018) who were classified as Australian-born or newly-arrived Asian-born MSM, and had HIV subtyping data available.

The study population was also stratified by place of acquisition (locally-acquired vs overseas-acquired) to compare differences in subtype acquisition.

Cases in the surveillance dataset for whom these criteria could not be established due to missing or incomplete data were excluded from the study population.

### Data analysis

The study population was characterised through a descriptive analysis using frequencies and percentages, and medians and interquartile ranges (IQR) as appropriate.

To compare the two groups of interest within the study population relevant variables from the surveillance dataset were analysed using chi-squared or Fisher's exact test as appropriate (categorical variables) or the Mann-Whitney U test (continuous variables). Exact binomial confidence intervals were calculated for proportions. *P* values <0.05 considered statistically significant. Due to the low number of cases for certain variables, some data fields collected in the surveillance dataset were combined for the purposes of analysis where appropriate to do so.

### Ethics

Ethics approval was granted by the Australian National University Human Research Ethics Committee on 7 January 2019 (2018/799). Individual patient consent was not required or sought as all data were collected under the Public Health and Wellbeing Act 2008.<sup>25</sup>

### Results

A total of 444 HIV cases notified between 1 January 2015 – 31 December 2018 were included in the study population. Of these cases 84% (371/444) were classified as locally-acquired and 16% (73/444) as overseas-acquired.

#### Clinical and epidemiological characteristics of locally-acquired cases

Of the locally-acquired cases, 267 (72%) were classified as Australian-born MSM and 104 (28%) as newly-arrived Asian-born MSM. There was a small increase in the proportion of newly-arrived Asian-born cases in the study population over the study period, from 26% in 2015 to 30% in 2018 (*P*=0.61).

Newly-arrived Asian-born cases were younger at diagnosis than Australian-born cases (median age 29 years vs 32 years, *P*=0.02), more frequently reported speaking a language other than English at home (39% vs 5%, *P*<0.001), more often resided in inner-Melbourne (46% vs 34%) and less often in regional Victoria (1% vs 14%, *P*<0.001).

Compared to Australian-born cases, newly-arrived Asian-born cases had a lower median CD4+ cell count at the time of diagnosis (365 vs 449 cells/ $\mu$ L, *P*=0.009). A greater proportion of newly-arrived Asian-born cases reported screening for STIs as their reason for testing (55%

versus 38%) and a lesser proportion reported screening for PrEP prescription (0% vs 2%). The characteristics of the study population are detailed in Table 1.

*Table 3. Characteristics of cases in the Australian-born (n=267) and newly-arrived Asian-born (n=104) MSM populations with newly-diagnosed, locally-acquired HIV infections over the study period 2015-2018.*

	Aus-born			Asian-born			P value
	n	%	95% CI	n	%	95% CI	
<b>Age (years) - Median (IQR)</b>	<b>32</b>	<b>26-42</b>	<b>-</b>	<b>29</b>	<b>25-35.5</b>	<b>-</b>	<b>0.02</b>
<b>Area of Residence *</b>							<b>0.002</b>
Inner Melbourne	87	34%	28-40%	44	46%	36-56%	
Middle Melbourne	73	29%	23-34%	30	31%	22-42%	
Outer Melbourne	59	23%	18-29%	21	22%	14-31%	
Regional Victoria	37	14%	10-19%	1	1%	0-6%	
<b>Language Spoken at Home</b>							<b>&lt;.001</b>
English	211	95%	91-98%	57	61%	51-71%	
Other	11	5%	2-9%	36	39%	29-49%	
<b>Reason for Testing</b>							0.18
Screening for STIs	102	39%	33-45%	56	55%	45-65%	
Investigation of symptoms suggestive of HIV	41	16%	11-20%	11	11%	6-18%	
Partner with HIV	16	6%	4-10%	5	5%	2-11%	
Reported recent risk behaviour	31	12%	8-16%	6	6%	2-12%	
Confirmation of HIV positive status	6	2%	1-5%	2	2%	0-7%	
PrEP screening	5	2%	1-4%	0	0%	0-4%	
Immigration screening	1	0.4%	0-2%	1	1%	0-5%	
Other	14	5%	3-9%	6	6%	2-12%	
Multiple reasons	48	18%	14-23%	15	15%	8-23%	
<b>CD4+ Cell Count at Diagnosis (cells/μL) - Median (IQR)</b>	<b>449</b>	<b>312-654</b>	<b>-</b>	<b>365</b>	<b>270-490</b>	<b>-</b>	<b>0.009</b>
<b>HIV-1 Subtype</b>							<b>&lt;.001</b>
Non-B subtype	55	21%	16-26%	62	60%	50-69%	
B-subtype	212	79%	74-84%	42	40%	31-50%	
<b>Clinical Status at Diagnosis</b>							0.48
Asymptomatic for HIV	192	90%	85-93%	80	87%	78-93%	
Symptomatic for HIV	22	10%	7-15%	12	13%	7-22%	
<b>HIV seroconversion illness in 12 months prior</b>							0.84
Yes	61	28%	22-35%	23	27%	18-38%	
No	155	72%	65-78%	62	73%	62-82%	

\* Based on local government area at time of diagnosis:

Inner Melbourne - Yarra, Stonnington, Melbourne, Port Phillip

Middle Melbourne - Banyule, Bayside, Boroondara, Darebin, Glen Eira, Hobsons Bay, Kingston, Manningham,

Maribyrnong, Monash, Moonee Valley, Moreland, Whitehorse

Outer Melbourne - Brimbank, Frankston, Greater Dandenong, Knox, Maroondah, Mornington Peninsula, Nillumbik,

Yarra Ranges, Cardinia, Casey, Hume, Melton, Whittlesea, Wyndham

Regional Victoria – all other non-metropolitan local government areas

### Subtype characteristics of locally-acquired cases

A total of 13 distinct HIV-1 subtypes, CRFs and URFs were observed in the study population including four pure subtypes (n=271, 73%), five CRFs (n=94, 25%) and four URFs (n=6, 2%).

Among the nine subtypes, CRFs and URFs observed in Australian-born cases over the study period, subtype B predominated (n=212, 79%) followed by CRF01\_AE (n=32, 12%), subtype C (n=11, 4%), CRF02\_AG (n=3, 1%), subtype A1 (n=2, <1%) and URFs B/CRF57\_BC, B/CRF01\_AE and 07\_BC/C/57\_BC (each n=1, <1%). Of the nine subtypes, CRFs and URFs observed in newly-arrived Asian-born cases, subtype CRF01\_AE was the most common (n=49, 47%) followed by subtype B (n=42, 40%), CRF07\_BC (n=5, 5%), subtype C (n=3, 3%), subtype G (n=1, <1%), CRFs



CRF12\_BF, CRF33\_01B (both n=1, <1%) and URFs B/F1 and 07\_BC/C/57\_BC (both n=1, <1%). A summary of the major subtypes, CRFs and URFs in each population over the study period is presented in Figure 1.

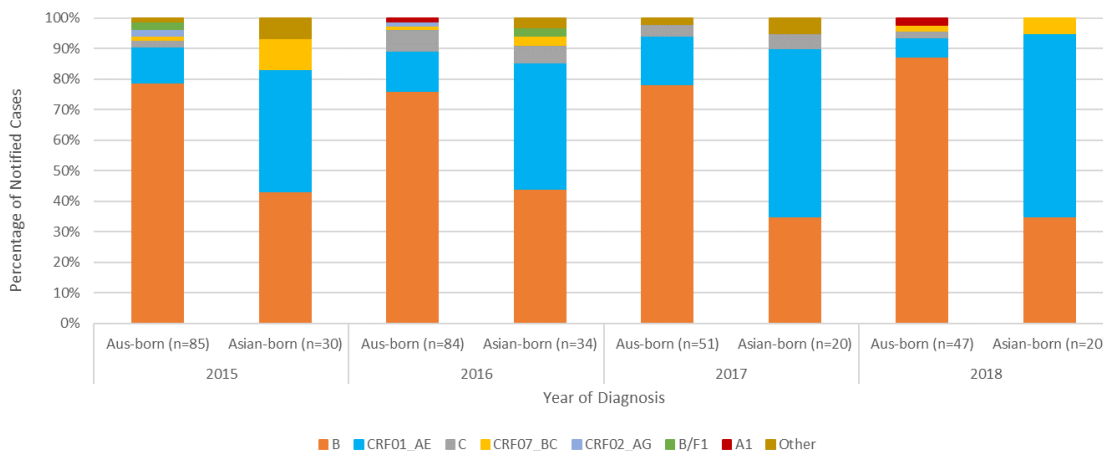


Figure 1. HIV-1 subtypes observed in cases in the Australian-born (n=267) and newly-arrived Asian-born (n=104) MSM populations with newly-diagnosed, locally-acquired HIV infections over the study period 2015-2018. Subtypes with two or more cases over the study period are shown individually. "Other" comprises six distinct forms that occurred only once in the study period.

Subtype diversity declined slightly over the study period; nine distinct forms were observed in 2015, eight in 2016, and five in each of 2017 and 2018. There was no significant change in the proportion of B and non-B subtypes in either the Australian-born ( $P=0.76$ ) or newly-arrived Asian-born ( $P=0.66$ ) populations over the study period.

Newly-arrived Asian-born cases were more frequently infected with a non-B subtype than Australian-born cases (60% versus 21%,  $P<0.001$ ). Of the newly-arrived Asian-born cases, 40% (n=42) were infected with subtype B, the most common subtype in Australian-born cases. Among Australian born cases 21% (n=55) were infected with a non-B subtype. CRF01\_AE was the most common non-B subtype in the Australian-born population and was the most common subtype in newly-arrived Asian-born cases.

#### Characteristics of overseas-acquired cases

Of the overseas-acquired cases, 52% (38/73) were Australian-born and 48% (35/73) were newly-arrived Asian-born MSM.

Among Australian-born cases, non-B subtypes accounted for a larger proportion of overseas-acquired infections compared to locally-acquired infections (58% vs 21%,  $P<.001$ ). The most

common overseas-acquired non-B subtype in Australian-born MSM was CRF01\_AE (14/22, 64%).

Among the Asian-born cases, subtype B accounted for a larger proportion of locally-acquired infections compared to the overseas-acquired infections (40% vs 29%,  $p=0.21$ ). The most common overseas-acquired subtype in newly-arrived Asian-born MSM was CRF01\_AE (17/35, 49%) (Figure 2).

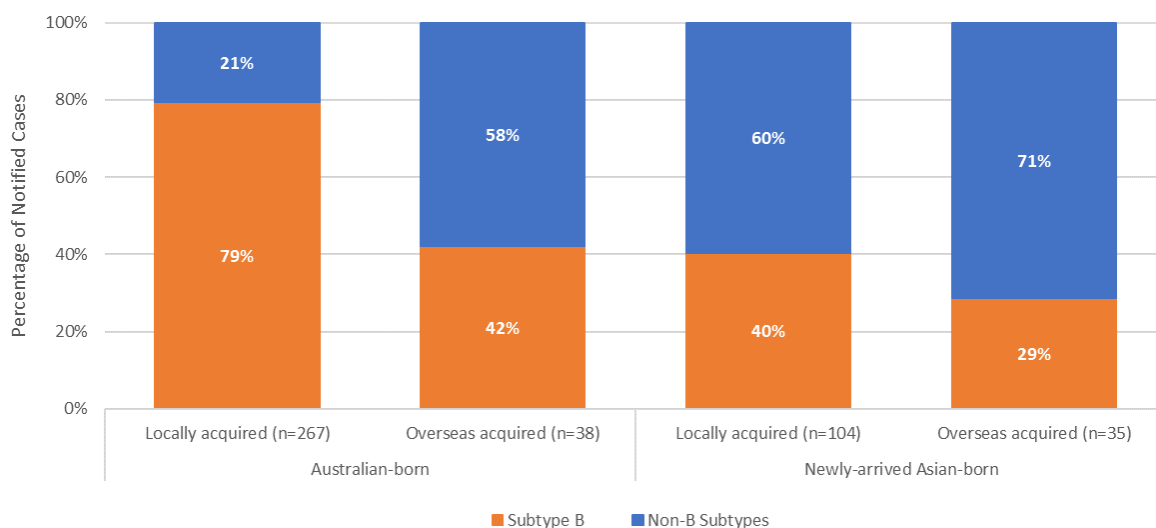


Figure 2. Proportions of HIV-1 B and non-B subtypes in the Australian-born and newly-arrived Asian-born MSM populations over the study period 2015-2018, by place of acquisition.

## Discussion

This study found the majority of locally-acquired HIV infections were subtype B (79%) in Australian-born and non-B (60%) in newly-arrived Asian-born MSM. These findings provide important biological data to support the theory, previously based on self-reported patient data, that local transmission in both populations is mostly assortative based on ethnicity.

However, the 40% of Asian-born MSM infected with subtype B and 21% of Australian-born infected with non-B subtypes may be suggestive of sexual mixing and local transmission between the two populations. This hypothesis is further supported by the greater proportion of subtype B infections acquired by newly-arrived Asian-born MSM in Australia, compared to infections acquired overseas. While assortative sexual mixing based on ethnicity is common, especially in newly-arrived communities, it is not surprising that sexual mixing occurs between men from these populations in the context of a large, multicultural, metropolitan city.

These observations are important to the control of HIV in Victoria, as many newly-arrived Asian-born MSM do not have access to publicly funded sexual health services, have low sexual health and risk reduction knowledge, come from cultures where male to male sex is

significantly stigmatised or criminalised, and do not identify with or connect into the local gay community and its associated resources and collective knowledge.<sup>11</sup>

This study also identified several significant differences in HIV epidemiology between the two populations including area of residence within Victoria, language other than English spoken at home and median CD4+ cell count at diagnosis. These findings are broadly consistent with a recent clinic-based study of similar populations in Victoria and New South Wales, and a previous Australian study that identified culturally and linguistically diverse HIV cases were significantly less likely to have started ART within six months of diagnosis, irrespective of their CD4 cell count.<sup>8, 26</sup>

A small majority of newly-arrived Asian-born MSM in this study lived in middle to outer suburbs of Melbourne, while Victoria's only sexual health service that does not require access to the publicly funded Medicare system is in inner-city Melbourne. This could mean there are individuals living with undiagnosed HIV in areas of Melbourne not well-served by a free-to-access sexual health service. Further research may be required to assess the level of access to culturally appropriate HIV services in middle, outer and regional areas where many newly-arrived Asian-born MSM live, work or study. This could include educational institutions with large Asian-born student populations in the middle to outer suburbs and regional centres.

There were several limitations to this study. The retrospective use of routine surveillance data means that the veracity of the case data (such as the likely place of acquisition and sexual exposures) could not be verified. Although the data is suggestive of sexual mixing and transmission between populations, the small sample size and resulting small numbers of cases within subgroups and the relatively short four-year study period made it difficult to draw firm conclusions on trends in transmission. The use of HIV subtyping analysis alone to make inferences on transmission is also relatively limited - in the future, routine genomic sequencing of all HIV isolates would be useful to facilitate detailed, high-resolution studies combining epidemiological and phylogenetic surveillance data. Such studies would better elucidate local transmission dynamics within Victoria's MSM populations.

Victoria has made strong progress toward the elimination of HIV. If this is to continue, public health authorities and the research community must better understand the prevention, testing and treatment needs of the growing newly-arrived Asian-born MSM population and address them in a culturally appropriate manner.

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# Oral Presentation at the International Union Against Sexually Transmitted Infections Asia Pacific Conference - Shanghai, China

25 October 2019

Australian National University

HIV-1 epidemiology and subtype diversity in the Australian-born and newly-arrived Asian-born men who have sex with men populations in Victoria, Australia 2015-2018

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### The Setting – Victoria, Australia

Population ~ 6.4 million. Melbourne ~ 5 million.

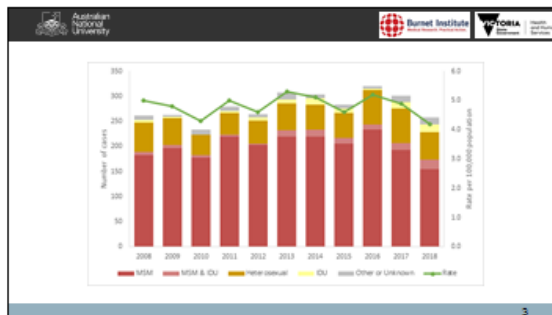
Increasing temporary international student population (200,000+ in 2018)

Top 10 countries of origin for post-secondary international students in 2018:

1. China
2. India
3. Malaysia
4. Vietnam
5. Sri Lanka
6. Nepal
7. Colombia
8. Indonesia
9. Thailand
10. Pakistan

Decreasing HIV diagnoses in Australian-born MSM. Increasing in Asian-born.\*

\* MacLennan et al. 2018



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Medical Research Institute

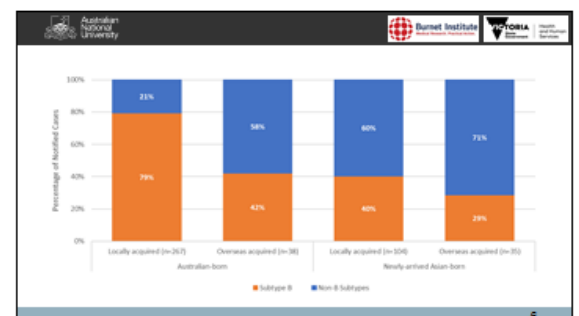
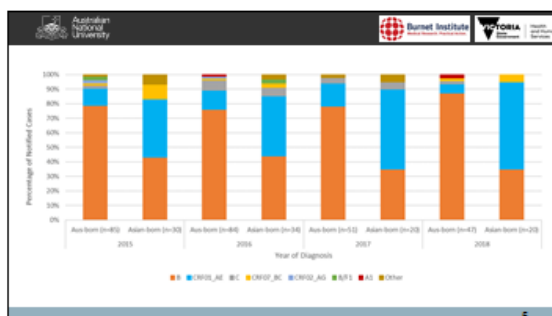
VICTORIA  
State Government  
Health and Human Services



### The Study Population (N=371)

Newly-diagnosed MSM HIV cases notified in Victoria 2015-2018.

Subtyping and epidemiological data available.

Australian-born (n=267) or newly-arrived Asian-born (n=104).



 Australian National University  Burnet Institute  VICTORIA

### Conclusions

Newly-arrived Asian-born MSM – barriers to prevention, diagnosis, treatment.

Need to improve our understanding of HIV transmission in this population.

Address prevention, testing and treatment needs in culturally appropriate manner.

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### Acknowledgements

Burnet Institute

Victorian Department of Health and Human Services

Victorian Infectious Diseases Reference Laboratory

Notifying medical practitioners

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## Appendix 1. ACCESS Activity Performance Indicators and Required Activities – Health Surveillance Fund 2016-2019

### ACCESS - Activity Performance Indicators – Health Surveillance Fund 2016-2019

#	Activity	Activity Detail	Information Source(s)	Performance Indicator(s)
1	Project Establishment	Submit a work plan and budget, recruit project staff and develop a project evaluation plan.	<ul style="list-style-type: none"> <li>▪ Internal documentation</li> <li>▪ Stakeholder interviews</li> </ul>	<ul style="list-style-type: none"> <li>▪ Submitted to and accepted by the Department of Health.</li> </ul>
2	Expand the ACCESS network	Expand ACCESS networks to all jurisdictions through the Laboratory Network, Sexual Health Service (SHS) Network and the Primary Health and High Caseload Service (PHHCS) Network.	<ul style="list-style-type: none"> <li>▪ Internal documentation</li> <li>▪ Stakeholder interviews</li> </ul>	<ul style="list-style-type: none"> <li>▪ At least 1 major SHS recruited from each jurisdiction within the agreed timeframe.</li> <li>▪ At least 2 key clinics (PHHCS) in most jurisdictions but a minimum of one in all jurisdictions, within the agreed timeframe.</li> <li>▪ At least 4 labs recruited in each of NSW and VIC, 3 in QLD, 1 in each of other jurisdictions (exc. TAS) within the agreed timeframe.</li> </ul>
3	Programs and procedures in place for data extraction, review and analysis from each site.	Electronically extract clinic consultation and diagnostic test data from existing patient management information systems at participating clinics, and BBV/STI testing data from participating laboratory sites.	<ul style="list-style-type: none"> <li>▪ Internal documentation</li> <li>▪ Stakeholder interviews</li> </ul>	<ul style="list-style-type: none"> <li>▪ GRHANITE™ successfully installed at all recruited sites within the agreed timeframes.</li> <li>▪ Data is extracted from all recruited sites and analysis completed within the agreed timeframes.</li> </ul>
4	Report on test outcomes in priority populations	Testing rate and proportion positive for BBVs (HIV, HBV and HCV) and STIs (chlamydia, gonorrhoea and syphilis) in gay and bisexual men, people who inject drugs, sex workers, the CALD populations and Aboriginal and young people (as relevant).	<ul style="list-style-type: none"> <li>▪ Kirby Annual Report</li> <li>▪ ACCESS data</li> <li>▪ Internal documentation</li> <li>▪ Stakeholder interviews</li> </ul>	<ul style="list-style-type: none"> <li>▪ Key indicator data for the goals and targets outlined in the National BBV and STI Surveillance and Monitoring Plan published in 2019 Kirby annual report.</li> </ul>



**ACCESS - Other Required Activities – Health Surveillance Fund 2016-2019**

Activity	Activity detail	Information source(s)
Ensure engagement with priority populations to inform the development of ACCESS	<ul style="list-style-type: none"> <li>▪ Expand engagement with relevant community organisations.</li> <li>▪ Actively seek input and feedback from priority populations.</li> <li>▪ Establish and maintain a national steering committee for ACCESS including representation from individuals and organisations relevant to each network.</li> </ul>	<ul style="list-style-type: none"> <li>▪ Internal documentation</li> <li>▪ Stakeholder interviews</li> </ul>
Undertake key analyses for each BBV and STI, for priority populations	<p>Key analyses should include:</p> <ul style="list-style-type: none"> <li>▪ Number of consults per patient per year</li> <li>▪ Characteristics of patients tested</li> <li>▪ Completeness of screening</li> <li>▪ Testing uptake</li> <li>▪ Testing frequency</li> <li>▪ Proportion testing positive</li> <li>▪ Assessment of care cascades (HIV and HCV)</li> <li>▪ Assessment of HBV immunity</li> </ul>	<ul style="list-style-type: none"> <li>▪ ACCESS data</li> <li>▪ Internal documentation</li> <li>▪ Stakeholder interviews</li> </ul>
Share results of analyses with stakeholders and the public	<p>Result should be shared via:</p> <ul style="list-style-type: none"> <li>▪ Annual routine reports for each network.</li> <li>▪ Site-specific reports to participating sites.</li> </ul>	<ul style="list-style-type: none"> <li>▪ Published reports</li> <li>▪ Peer reviewed publications and abstracts</li> </ul>

	<ul style="list-style-type: none"> <li>▪ Newsletters to government, community and other stakeholders.</li> <li>▪ Provision of data to key national and jurisdictional government reports.</li> <li>▪ Regular presentation of results and emerging trends at key forums.</li> <li>▪ Analysis and publication of key results in peer-reviewed journals.</li> <li>▪ Provision of data to governments and other interested parties for further analysis.</li> <li>▪ Publication of de-identified data on the ACCESS website.</li> </ul>	<ul style="list-style-type: none"> <li>▪ Media/communications materials</li> <li>▪ ACCESS website</li> <li>▪ Stakeholder interviews</li> </ul>
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## Appendix 2. Peer-reviewed publications using ACCESS data, 2016-2019

2019

**Sexually transmissible infections among transgender men and women attending Australian sexual health clinics.** Callander D, Cook T, Read P, Hellard ME, Fairley CK, Kaldor JM, Vlahakis E, Pollack A, Bourne C, Russell DB, Guy RJ, Donovan B *Med J Aust.* 2019 August; Epub ahead of print

**A comparative, retrospective analysis of HIV testing among gay, bisexual and other men who have sex with men in Melbourne, Australia.** Ryan KE, Wilkinson AL, Chow E, Read T, Chen M, Locke P, Leitinger D, Bradshaw C, Pedrana A, Hellard M, Fairley CK, Stoové M *Aust N Z J Public Health.* 2019 May; Epub ahead of print

**Assessment of service refinement and its impact on repeat HIV testing by client's access to Australia's universal healthcare system: a retrospective cohort study.** Ryan KE, Wilkinson AL, Asselin J, Leitinger DP, Locke P, Pedrana A, Hellard M, Stoové M. *J Int AIDS Soc.* 2019 Aug;22(8):e25353

**Association of HIV Preexposure Prophylaxis with Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection.** Traeger MW, Cornelisse VJ, Asselin J, Price B, Roth NJ, Willcox J, Tee BK, Fairley CK, Chang CC, Armishaw J, Vujovic O, Penn M, Cundill P, Forgan-Smith G, Gall J, Pickett C, Lal L, Mak A, Spelman TD, Nguyen L, Murphy DA, Ryan KE, El-Hayek C, West M, Ruth S, Batrouney C, Lockwood JT, Hoy JF, Hellard ME, Stoové MA, Wright EJ; PrEPX Study Team *JAMA.* 2019 Apr; 321(14):1380-1390

**Gonorrhoea gone wild: rising incidence of gonorrhoea and associated risk factors among gay and bisexual men attending Australian sexual health clinics.** Callander D, Guy R, Fairley CK, McManus H, Prestage G, Chow EPF, Chen M, Connor CCO, Grulich AE, Bourne C, Hellard M, Stoové M, Donovan B *Sex Health.* 2019 Jan; Epub ahead of print

**Early initiation of antiretroviral therapy for people newly diagnosed with HIV infection in Australia: trends and predictors, 2004-2015.** McManus H, Callander D, Donovan B, Russell DB, O'Connor CC, Davies SC, Lewis DA, Hellard ME, Chen MY, Petoumenos K, Varma R, Cogle A, Boyd MA, Grulich A, Pollard J, Medland N, Fairley CK, Guy RJ *Med J Aust.* 2019 Feb; 210(6):269-275

**Can Australia reach the World Health Organization Hepatitis C elimination goal by 2025 among HIV-positive gay and bisexual men?** Boettiger DC, Salazar-Vizcaya L, Dore GJ, Gray RT, Law MG, Callander D, Lea T, Rauch A, Matthews GV, 2019, *Clin Infect Dis*, <http://dx.doi.org/10.1093/cid/ciz164>

2018

**Monitoring the Control of Sexually Transmissible Infections and Blood-Borne Viruses: Protocol for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS).** Callander D, Moreira C, El-Hayek C, Asselin J, van Gemert C, Watchirs Smith L, Nguyen L, Dimech W, Boyle DI, Donovan B, Stoové M, Hellard M, Guy R JMIR Res Protoc. 2018 Nov; 7(11): e11028

**Assessing the Impacts of Integrated Decision Support Software on Sexual Orientation Recording, Comprehensive Sexual Health Testing, and Detection of Infections Among Gay and Bisexual Men Attending General Practice: Observational Study.** Callander D, Bourne C, Wand H, Stoové M, Hocking JS, de Wit J, Kaldor JM, Donovan B, Pell C, Finlayson R, Baker D, Forssman B, Tee BK, Kefalas B, Duck T, Guy R JMIR Med Inform. 2018 Nov; 6(4):e10808

**Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study.** Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, Schmidt HMA, Zablotska I, Price K, Whittaker B The Lancet HIV, vol. 5, pp. e629 - e637

**Understanding the Targeting and Uptake of HIV Testing Among Gay and Bisexual Men Attending Sexual Health Clinics.** Jamil MS, McManus H, Callander D, Prestage G, Ali H, O'Connor CC, Chen M, McNulty AM, Knight V, Duck T, Keen P, Gray J, Medland N, Hellard M, Lewis DA, Grulich AE, Kaldor JM, Fairley CK, Donovan B, Guy RJ; ACCESS and NSW Partnership Project Steering Committees. AIDS Behav. 2018 Jan; 22(2):513-521

**Rising Chlamydia and Gonorrhoea Incidence and Associated Risk Factors Among Female Sex Workers in Australia: A Retrospective Cohort Study.** Callander D, McManus H, Guy R, Hellard M, O'Connor CC, Fairley CK, Chow EPF, McNulty A, Lewis DA, Carmody C, Schmidt HA, Kim J, Donovan B Sex Transm Dis. 2018 Mar; 45(3):199-206

**Evaluation of PrEP eligibility criteria using sexually transmissible infections as HIV risk markers at enrolment in PrEPX, a large Australian HIV pre-exposure prophylaxis trial.** Cornelisse VJ, Fairley CK, Stoove M, Asselin J, Chow EPF, Price B, Roth NJ, Willcox J, Tee BK, Penn M, Chang CC, Armishaw J, Forgan-Smith G, Wright EJ; PrEPX study team Clin Infect Dis. 2018 Nov; 67(12):1847-52

**Implications of survey labels and categorisations for understanding drug use in the context of sex among gay and bisexual men in Melbourne, Australia.** Ryan KE, Wilkinson AL, Pedrana A, Quinn B, Dietze P, Hellard M, Stoové M Int J Drug Policy. 2018 May; 55:183-186

**The 2016 HIV diagnosis and care cascade in New South Wales, Australia: Meeting the UNAIDS 90-90-90 targets.** Keen P, Gray RT, Telfer B, Guy R, Schmidt HM, Whittaker B, Holden J, Holt M, Kelleher A, Wilson D, 2018, Journal of the International AIDS Society, vol. 21

**People Born in Non-Main English Speaking Countries Are Less Likely to Start Hiv Treatment Early In Australia: A National Cohort Analysis, 2014-15.** Gunaratnam P, McManus H, Watchirs-Smith L, McGregor S, Callander D, Brown G, Lobo R, O'Connor CC, Hellard M, Medland N, Lewis D, Palmer C, Law M, Gray R, Donovan B, Guy R; ACCESS Steering Committee J Acquir Immune Defic Syndr. 2018 Feb; 77(3): e31-e34

**The changing pattern of sexually transmissible infections and HIV diagnosed in public sexual health services compared with other locations in New South Wales, 2010-14.** Bourne C, Lam M, Selvey C, Guy R, Callander D, 2018, Sexual Health, vol. 15, pp. 366 – 369

**Protocol for an HIV Pre-Exposure Prophylaxis (PrEP) Population Level Intervention Study in Victoria Australia: The PrEPX Study.** Ryan KE, Mak A, Stooze M, Price B, Fairley CK, Ruth S, Lal L, Asselin J, El-Hayek C, Nguyen L, Batrouney C, Wilson D, Lockwood J, Murphy D, Cornelisse VJ, Roth N, Willcox J, Chang CC, Armishaw J, Tee BK, Penn M, Forgan-Smith G, Williams C, Montgomery J, Byron K, Coelho A, Allen B, Wiggins J, Kelsall J, Vujovic O, West M, Pierce AB, Gallant D, Bell C, de Wit JBF, Hoy JF, Wesselingh SL, Grant RM, Wright EJ Front Public Health. 2018 May; 6:151

## **2017**

**A cross-sectional study of HIV and STIs among male sex workers attending Australian sexual health clinics.** Callander D, Read P, Prestage G, Minichiello V, Chow EP, Lewis DA, McNulty A, Ali H, Hellard M, Guy R, Donovan B Sex Transm Infect. 2017 Jun; 93(4):299-302

**Increased syphilis testing of men who have sex with men: greater detection of asymptomatic early syphilis and relative reduction in secondary syphilis.** Chow EPF, Callander D, Fairley CK, Zhang L, Donovan B, Guy R, Lewis DA, Hellard M, Read P, Ward A, Chen MY; ACCESS collaboration. Clin Infect Dis. 2017 Aug; 65(3):389-395

**Hepatitis C testing and re-testing among people attending sexual health services in Australia, and hepatitis C incidence among people with human immunodeficiency virus: analysis of national sentinel surveillance data.** Boettiger DC, Law MG, Dore GJ, Guy R, Callander D, Donovan B, O'Connor CC, Fairley CK, Hellard M, Matthews G BMC Infect Dis. 2017 Dec; 17(1):740

**Human papillomavirus vaccination and genital warts in young indigenous Australians: National sentinel surveillance data.** Ali H, McManus H, O'Connor CC, Callander D, Kong M,

Graham S, Saulo D, Fairley CK, Regan DG, Grulich A, 2017, Medical Journal of Australia, vol. 206, pp. 204 - 209

## **2016**

**A longitudinal cohort study of HIV 'treatment as prevention' in gay, bisexual and other men who have sex with men: The Treatment with Antiretrovirals and their Impact on Positive and Negative men (TAIPAN) study protocol.** Callander D, Stoové M, Carr A, Hoy JF, Petoumenos K, Hellard M, Elliot J, Templeton DJ, Liaw S, Wilson DP, Grulich A, Cooper DA, Pedrana A, Donovan B, McMahon J, Prestage G, Holt M, Fairley CK, McKellar-Stewart N, Ruth S, Asselin J, Keen P, Cooper C, Allan B, Kaldor JM, Guy R BMC Infect Dis. 2016 Dec; 16(1):752

**Does Living Outside of a Major City Impact on the Timeliness of Chlamydia Treatment? A Multicenter Cross-Sectional Analysis.** Foster R, Ali H, Crowley M, Dyer R, Grant K, Lenton J, Little C, Knight V, Read P, Donovan B, 2016, Sexually Transmitted Diseases, vol. 43, pp. 506 - 512

## Appendix A

### Communication to a Non-Scientific Audience

This appendix contains three participant information documents that I prepared for Barwon Health to use in the case-control study component of the NHMRC Partnership Project funded *Beating Buruli in Victoria* project.

The *Beating Buruli in Victoria* project is a two-year collaborative research partnership between the Victorian Department of Health and Human Services, the Doherty Institute, Barwon Health, Austin Health, CSIRO, Agriculture Victoria, the University of Melbourne and Mornington Peninsula Shire.

The case-control component of the *Beating Buruli in Victoria* project is being conducted by Barwon Health and the CSIRO, with support from the other project partners. It aims to identify modifiable behavioural and environmental factors that may be associated with Buruli ulcer in Victoria, and to provide new information about the presence of *Mycobacterium ulcerans* in the environment of affected areas. Data for the study will be collected through phone-based interviews and residential environmental surveys.

The purpose of the participant information materials was to provide potential study participants with understandable information on Buruli ulcer and the case-control study to allow them to make an informed decision on whether to participate.



## Controlling Buruli ulcer in Victoria: Case control study Buruli Ulcer Information Sheet

### What is Buruli ulcer?

Buruli ulcer is a skin disease caused by the bacterium *Mycobacterium ulcerans*. The toxins made by the bacteria destroy skin cells, small blood vessels and the fat under the skin, which leads to localised swelling or the formation of a lesion. It can initially be mistaken for an insect bite or spider bite and can sometimes be itchy.

### What are the symptoms of Buruli ulcer?

The symptoms of Buruli ulcer infection usually progress slowly over several weeks or months, although occasionally it can progress rapidly. It can occur anywhere on the body, but it is most common on exposed areas of the limbs and over joints.

- Initially, a small spot that looks like a mosquito or spider bite forms on or under the skin.
- The spot usually gets bigger over days or weeks and may form a crusty, non-healing scab.
- Over time the spot breaks down into a destructive ulcer that continues to increase in size and is surrounded by a ring of red swelling.

In most cases, Buruli ulcers are painless and there is generally no fever or other signs of infection. However, a small number of cases experience fever and pain. The infection may sometimes present with no ulceration but with localised pain, swelling and fever, raised lumps, or thickened or raised flat areas of skin.

### How do people get Buruli ulcer?

The bacteria that cause Buruli ulcer are found in the environment and have been detected in mosquitoes, vegetation and poo from some possum species in areas affected by Buruli ulcer. Buruli ulcer has also been observed in animals including possums, dogs, cats, alpacas, horses and koalas.

It is not yet known exactly how humans become infected with the bacteria, or where in the environment the bacteria prefer to live. It is not thought to be spread person-to-person.



### Could my pet get Buruli ulcer?

Buruli ulcer is very rare in dogs, cats and other domestic animals, but treatment is available. If you are concerned about your pet, please seek advice from your veterinary practitioner.

### How long does it take for the symptoms of Buruli ulcer to appear?

It is estimated that in Victoria, the average time from exposure to the bacteria to the onset of first symptoms is about 4.5 months but can range from 2 to 9 months.

### In what areas of Victoria do people get Buruli ulcer?

Buruli ulcer occurs in restricted geographic areas of Victoria. The following areas are affected:

- Bellarine Peninsula
- East Gippsland
- Frankston region
- Mornington Peninsula
- Philip Island
- South-eastern bayside suburbs

Currently, most cases occur in residents and visitors to the Bellarine and Mornington peninsulas.

### Does Buruli ulcer occur anywhere else outside Victoria?

Buruli ulcer has been reported in 33 countries around the world. Affected areas include West Africa, Central Africa, New Guinea, Latin America and tropical regions of Asia.

Within Australia, Buruli ulcer also occurs in the Daintree region of Far North Queensland.

### Who is most at risk of getting Buruli ulcer?

People who live in or visit the affected areas of Victoria are considered at greatest risk of infection.

People of any age can be infected. In Victoria, more cases are reported in people aged 60 years and over compared to other age groups.

### How many people get Buruli ulcer each year?

2017, a total of 275 cases were notified to the Victorian Department of Health and Human Services, the highest annual total on record and a 51% increase compared to 2016.

Communities around Port Phillip Bay are currently experiencing a worsening epidemic of this disease. As well as an increasing number of cases, an increasing proportion of cases are severe in nature.

### What has caused the increase in cases of Buruli ulcer?

The cause of the increase in Buruli ulcer cases is currently unknown. It is anticipated that the results of this study may provide new information to allow for the development of effective ways to prevent infections and stop the epidemic.



## How is Buruli ulcer diagnosed and treated?

Buruli ulcer is usually diagnosed by a doctor, based on:

- where you live – if you live in an area affected by Buruli ulcer
- your travel history – if you have travelled to an area affected by Buruli ulcer
- physical examination – to identify a slowly enlarging, painless ulcer or nodule
- swabs or biopsy taken from the ulcer, which are tested in a laboratory.

Buruli ulcers can usually be treated with oral antibiotics. Surgery is sometimes used in combination with antibiotic therapy. Regular dressings are usually required. Complete healing usually takes between 3 and 6 months depending on how big the ulcer is.

As ulcers get bigger over time, early diagnosis and effective treatment are important to minimise tissue loss and reduce the time until the ulcer heals.

## How can I avoid getting Buruli ulcer?

Although the exact cause of infection in humans is not known, it makes sense to protect yourself from potential sources of infection, such as soil where the bacteria can be naturally found, insect bites and traumatic wounds (e.g. puncture injuries from thorns).

Suggestions to reduce the risk of infection include:

- Wear gardening gloves, long-sleeved shirts and trousers when gardening or working outdoors.
- Avoid insect bites by using suitable insect repellents and long clothing, especially during the warmer months.
- Protect cuts or abrasions with sticking plasters.
- Promptly wash and cover any scratches or cuts you receive while working outdoors.
- See your doctor if you have a suspicious skin lesion.

It is important to remember that the overall risk of infection is low, even in the affected areas.





## **Controlling Buruli ulcer in Victoria: Case control study Participant Information Sheet**

This Participant Information Sheet will inform you about the case control study. It explains what is involved in the study to help you decide if you want to participate. Please read this information carefully, and if you have any further questions or would like more information, contact the study team using the details provided below.

### **What is this study about?**

Buruli ulcer is a skin disease caused by the bacterium *Mycobacterium ulcerans*. The toxins made by the bacteria destroy skin cells, small blood vessels and the fat under the skin, which can lead to the formation of a destructive ulcer. It can initially be mistaken for an insect bite or spider bite and can sometimes be itchy.

Communities around Port Phillip Bay are currently experiencing a worsening epidemic of this disease. As well as an increasing number of cases, an increasing number of cases are severe in nature. The bacteria that cause Buruli ulcer are found in the environment and have been detected in mosquitoes, vegetation and poo from some possum species in areas affected by Buruli ulcer. It is not yet known exactly how humans become infected with the bacteria, or where in the environment the bacteria prefer to live.

An important step toward controlling the epidemic is to develop a better understanding of the risk factors for contracting Buruli ulcer and determine effective ways to prevent infections.

### **What is the purpose of this study?**

This project aims to identify environmental and behavioural factors associated with Buruli ulcer in the affected areas of Victoria, and to provide new information about where the *Mycobacterium ulcerans* bacteria is found in the residential environment.

### **Why have I been selected to participate?**

You have been selected to participate in this study because you were either diagnosed with Buruli ulcer recently or you are a resident of an area affected by Buruli ulcer.

We obtained your details from either the Australian Electoral Commission, the Victorian Population Health Survey or the Public Health Event Surveillance System (this records people with particular diseases, who have



been notified to the Victorian Department of Health and Human Services by laboratories and medical practitioners as required under the *Public Health and Wellbeing Act 2008*).

To get the most out of this study, we need everyone selected to participate, regardless of whether or not they have had Buruli ulcer. It is equally important to have both participants that have had Buruli ulcer (cases) and those who have not (controls).

### What is involved in participating?

Participation in the study is completely voluntary. There are no costs associated with participation, and you will not be paid to participate.

All participants will be asked to self-complete a short questionnaire. This should take no more than 30 minutes of your time. You can return the completed questionnaire in the reply-paid envelope. If you need any help with the questionnaire you can ask someone you know, or you can contact the study team using the contact details provided below.

In the questionnaire, we will also ask if you would be willing to be contacted about a residential field survey. If you agree to be contacted, we will ask you to allow a study team access to your property for two residential field surveys, approximately six months apart. Each survey visit is expected to take about one hour and can be on a day and time that suits you. For more information on what is involved in the field survey, please see the attached *Residential Field Survey Participant Information Sheet*.

As a participant, you can withdraw your consent at any time after enrolling in the study by contacting the study team. If you withdraw after you have completed the questionnaire or the field survey, your answers will be removed and not included in the results.

### How will the results of the study be used?

Once collected, all questionnaire responses will be combined with those of other participants, and with data from the field surveys. Identifying information (such as name and address) will be removed to protect individual privacy. The combined data will be analysed to determine what behavioural and environmental factors may be associated with Buruli ulcer.

Results will also be used to inform the other components of the research project to work out which communities are most at risk of Buruli ulcer both now and in the future and to inform a mosquito control study and the development of other intervention strategies against this disease.

All findings will be made publicly available, but only grouped (non-identifiable) results will be presented. This will include publications in both the scientific literature and the popular media.

Participants can elect to receive a summary of results by post or email by providing these contact details on the study questionnaire. Results from individuals or individual properties will not be released.

### Are there any risks and/or benefits associated with participating?

We will not ask you any personal questions that are not relevant to this study. During the study, you can refuse any question you do not wish to answer. There are no invasive procedures or tests involved.

While you may not receive any personal benefit from your participation, the results from this study will help to inform the development of effective interventions to reduce or prevent further cases of Buruli ulcer in Victoria.





If you decide to participate in the field study and agree to have a mosquito trap left at your property, then you may experience less mosquito bites during this time. Unfortunately, this effect will only be temporary.

### Has this study been reviewed and approved for ethics?

This study has been approved by the Victorian Department of Health and Human Services human research ethics committee.

You can discuss your participation in this study with project staff, but if you would like to speak to an officer not involved with the study, please contact the Secretary of the ethics committee on:

Mr Jeffrey Chapman  
Secretary,  
Department of Health and Human Services  
Human Research Ethics Committee,  
Tel: (03) 9096 5239  
Email: [Jeffrey.chapman@dhhs.vic.gov.au](mailto:Jeffrey.chapman@dhhs.vic.gov.au)

### How will my confidentiality and privacy be protected if I participate?

During this study, some of your personal information will be collected. All information that is collected will be stored in secure buildings within password-protected computer files. Only members of the study team can access these files. We will not disclose any of your information or responses to anyone not directly involved in this research. Any collected information will only be used for this study.

Both paper and electronic documents will be kept for a minimum of seven years, in line with the Victorian *Public Records Act 1973*, after which time they will be securely destroyed.

### Who is conducting this study?

The study is being jointly conducted by Barwon Health and the Commonwealth Scientific and Industrial Research Organisation (CSIRO).

Additional support for the study is provided by Victorian Department of Health and Human Services, Mornington Peninsula Shire Council, Deakin University, University of Melbourne and AgriBio.

The study is funded by the National Health and Medical Research Council (NHMRC) and the Victorian Department of Health and Human Services.

### How can I get further information?

If you have any questions or would like some more information about the project, please do not hesitate to get in touch with the study team by contacting:

Dr Kim Blasdell  
Research Scientist  
03 5227 5261  
[Kim.Blasdell@csiro.au](mailto:Kim.Blasdell@csiro.au)

### What if I have medical concerns?

If participation in the study has resulted in any form of distress or you suspect that you may have Buruli ulcer, please contact or visit your GP.



## What should I do now?

To participate, please complete the attached questionnaire and return it using the replied paid envelope within one month of receipt. You can contact the project team using the details above if you want to review or edit your answers at any time.

If necessary, someone can help you answer this questionnaire, but your helper is kindly asked to avoid influencing your responses.

If you do not want to participate and do not want to be contacted again, please complete the opt-out form and return it using the replied paid envelope.

As Buruli ulcer is a notifiable disease, please note that if you have the disease, you may be contacted by the Department of Health and Human Services. This is part of the routine public health follow up for Buruli ulcer and is not related to this research.





## **Controlling Buruli ulcer in Victoria: Case control study Residential field survey participant information sheet**

### **What is involved in participating?**

Participation in the study is completely voluntary. There are no costs associated with participation, and you will not be paid to participate.

As a participant, you can withdraw your consent at any time after enrolling in the study by contacting the study team (see below for details). If you withdraw the information from your residence will be removed and not included in the results.

### **Who is conducting this study?**

The study is being jointly conducted by Barwon Health and the Commonwealth Scientific and Industrial Research Organisation (CSIRO). Additional support for the study is provided by Victorian Department of Health and Human Services, Mornington Peninsula Shire Council, Deakin University, University of Melbourne and AgriBio.

The study is a component of a larger research project funded by the National Health and Medical Research Council (NHMRC) and the Victorian Department of Health and Human Services that aims to understand how Buruli ulcer is transmitted and determine effective ways to prevent and reduce infections.

### **What will happen during the survey?**

Between two and four researchers from the Commonwealth Scientific and Industrial Research Organisation (CSIRO) will meet you at your property on a day and time of your choosing. They will arrive in a vehicle marked with either CSIRO, or the word 'Research'.

There will be two surveys at each property, approximately six months apart. Each survey should take about one hour.

### **What will be expected of me during the survey?**

You will be asked to meet the researchers at the property, and to remain on the property during the field survey (you can also designate another adult to do this for you).



You can ask the researchers to leave your property at any time, and you can have friends or family with you if you prefer.

You may be asked a few questions by the researchers, such as:

- How big is your property?
- Where do you spend the most time outside?
- Do you know what species of plants are in your garden?

### What information will they collect?

The researchers will aim to collect the following information:

- Location coordinates using a Global Positioning System (GPS).
- The type, number and location of plants, water sources and other significant features.
- The characteristics of the soil on your property (e.g. type, texture, pH and temperature).
- With your permission, photos or a video of the plants on your property (no photos or videos of people will be taken, and none will be published, they will be used for analysis purposes only).

### What samples will they collect?

The researchers will aim to collect the following samples:

- Small samples of soil (about a garden trowel's worth) by digging shallow holes (about 5-10cm deep).
- Small clippings from spiky or thorny plants and from plants that possums like to eat.
- Biting insects using an 'aspirator' (a small battery-operated, vacuum device).
- Samples of mammal poo (but not human!).
- Water samples from any available water sources (e.g. rainwater tanks, ponds, flower pots and gutters).
- Any mosquito larvae that are found in these water sources using a fine-mesh net. For rainwater tanks and gutters this will require access to the top of the tank or roof (don't worry, we'll bring our own ladder!).

### Do I have to do anything after the survey?

The researchers will place several insect sticky traps around your property. These need to be left in place for between two and ten days.

After this time, you will be asked to collect the sticky traps (whilst wearing latex free gloves that will be provided to you by the study team), place them in the provided reply-paid envelope and return them by post.

If you agree, the researchers may place a different kind of mosquito trap on your property. The researchers will need to return after a day or two to collect this.



### What happens to the samples collected from my property?

All samples will be taken back to either the CSIRO Australian Animal Health Laboratory or the Victorian Government AgriBio laboratory, where they will be tested for the bacteria that cause Buruli ulcer.

### Will I find out the results of the samples collected from my property?

All participants in a residential field survey can elect to receive a summary of the field survey results at the end of the study by indicating this on the questionnaire. Results from individuals or individual properties will not be released.

The testing of samples and the analysis and interpretation of data can take some time, so please be patient.

### Will the results of the samples collected from my property be made public?

While the findings from the surveys will be made publicly available, only grouped data will be published, with no identifying information about the location of specific properties.

The findings will also be used to inform the other components of the research project including a mosquito control study and the development of other intervention strategies against this disease.

### Are there any risks and/or benefits associated with participating?

There are no expected risks to you or your family from participating in the study.

While you may not receive any personal benefit from your participation, the results from this study will help to inform the development of effective interventions to reduce or prevent further cases of Buruli ulcer in Victoria.

Due to the mosquito traps left at your property you may experience less mosquito bites during this time. Unfortunately, this effect will only be temporary.

### Has this study been reviewed and approved for ethics?

This study has been approved by the Victorian Department of Health and Human Services human research ethics committee.

You can discuss your participation in this study with project staff, but if you would like to speak to an officer not involved with the study, please contact the Secretary of the ethics committee on:

Mr Jeffrey Chapman  
Secretary,  
Department of Health and Human Services  
Human Research Ethics Committee,  
Tel: (03) 9096 5239  
Email: Jeffrey.chapman@dhhs.vic.gov.au





### How will my confidentiality and privacy be protected if I participate?

All information that is collected will be stored in secure buildings within password-protected computer files. Only members of the study team can access these files. We will not disclose any of your information to anyone not directly involved in this research. Any collected information will only be used for this study.

Both paper and electronic documents will be kept for a minimum of seven years, in line with the Victorian *Public Records Act 1973*, after which time they will be securely destroyed.

### Medical concerns

If participation in the study has resulted in any form of distress, or you suspect you may have Buruli ulcer, please contact or visit your GP.

### Contact details

If you have any questions or would like more information about the project, please do not hesitate to contact the study team on:

Dr Kim Blasdell  
Research Scientist  
03 5227 5261  
[Kim.Blasdell@csiro.au](mailto:Kim.Blasdell@csiro.au)



## Appendix B

### Summary of Teaching Activities

This appendix contains three teaching activities that I developed and delivered during the MAE:

1. A short introductory lecture on data visualisation, presented to the first-year 2019 MAE cohort at our third courseblock in March 2019. This lecture was prepared and presented alongside fellow 2018 cohort members Sophie Bowman-Derrick and Caroline Taunton. We had originally planned to include a practical demonstration of how to set up and visualise surveillance data using Microsoft PowerBI. Due to unforeseen technical issues with the PC in the tutorial room, we could only demonstrate the finished product. Feedback from the participants in the lecture was generally positive, with some expected negative responses regarding the technical issues in the PowerBI demonstration. A lesson from this experience is to always check prior to a lecture that the IT equipment available at the venue is compatible with the programs you plan to use.
2. An introductory lecture on the basics of social network analysis for infectious diseases. I was invited by the MAE staff to give this lecture to the 2018 cohort at the third courseblock in March 2019. As my own experience with social network analysis methods was limited (I had recently applied the concepts in one of my projects), I decided it was best to give a brief and straightforward overview, which would allow participants to reflect on how they may be able to make use of social network analysis in their own work. Although formal feedback on the lecture was not sought, anecdotal feedback from participants and MAE staff was positive.
3. A “Lesson from the Field” based on the epidemiological challenges of investigating tuberculosis clusters and outbreaks. I developed the lesson materials and distributed them to the participants; fellow 2018 MAE cohort members Stephen Harfield, Anthea Katelaris and Tamara Riley. Participants were asked to review the background reading and complete the exercises before the lesson. I facilitated the lesson via Zoom on 17 April 2019, where we discussed the participants responses to the exercises and recapped the key learnings. Feedback from the lesson was very positive, and participants enjoyed applying what they had learned in the background reading to the scenario-based exercises.

# Data Visualisation Lecture – 2019 MAE Cohort Teaching Exercise

Australian National University

## Data Visualisation

Sophie Bowman-Derrick  
Shaun Coutts  
Caroline Taunton

Australian National University

### Learning Objectives

- Gain an understanding of the importance of data visualisation
- Gain an awareness of the range of methods and approaches to data visualisation
- Understand the principles of effective data visualisation
- Be able to critically evaluate examples of data visualisation
- Have a basic understanding of interactive data visualisation tools

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### Today

- Hans Rosling
- What is data visualisation
- Types
- Interactive examples
- Why is data visualisation important
- Rate these
- Some data visualisation tools
- Demo
- Principles for presenting data

3

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### So you want to be an Epidemiologist?



**HANS ROSLING**  
(1948-2017)

<https://www.youtube.com/watch?v=Z814k0Q8e8Y>

4

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### What is data visualisation?

Why visualise data?

5

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### Is it new?



6

## Types of data visualisation

### Line listed data

id	age_group_bin	d_event_date	d_event_id	site_type	pathogen_name	event_date
14794	not new infection	19Apr2013	828118	QBH 02		3004 19 Apr 2013
14797	not new infection	04Jul2013	828120	QBH 02		3004 19 Apr 2013
14799	not new infection	23Oct2013	828121	QBH 02		3004 19 Apr 2013
14799	not new infection	19Jan2014	828122	QBH 02		3004 19 Apr 2013
14800	not new infection	23Apr2014	828124	QBH 02		3004 19 Apr 2013
14802	not new infection	01May2014	828127	QBH 02		3004 19 Apr 2013
14802	not new infection	01Apr2014	828131	QBH 02		3004 19 Apr 2013
14803	not new infection	14Feb2017	828134	QBH 02		3004 19 Apr 2013
14804	not new infection	14Mar2017	828136	QBH 02		3004 19 Apr 2013
14805	not new infection	10May2017	828139	QBH 02		3004 19 Apr 2013
14806	not new infection	23Aug2017	828141	QBH 02		3004 19 Apr 2013
14807	not new infection	20Nov2017	828143	QBH 02		3004 19 Apr 2013
14808	not new infection	23Mar2018	828144	QBH 02		3004 19 Apr 2013
14809	not new infection	30Mar2013	828196	QBH 02		3121 19 Apr 2013
14810	not new infection	09Aug2014	828192	QBH 02		3121 19 Apr 2013
14811	not new infection	18Jan2018	828194	QBH 02		3121 19 Apr 2013
14812	not new infection	22Apr2014	828193	QBH 02		3121 19 Apr 2013

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## Types of data visualisation

### Summary tables

Table 7. Annual syphilis positivity rate among MSM

	2012	2013	2014	2015	2016	2017	Trend	p-value
<b>Total (%)</b>								
All MSM	2.9	3.5	5.6	5.4	5.6	6.5	↑	<0.01
<b>HIV status (%)</b>								
HIV-positive MSM	4.6	5.5	8.2	7.2	7.2	5.3	■	0.32
HIV-negative MSM	1.7	1.5	2.2	3.1	3.3	3.8	↑	<0.01
<b>PrEP use (%)</b>								
On HIV PrEP	-	-	-	-	5.1	6.1	■	0.18
Not on HIV PrEP	-	-	-	-	2.2	2.0	■	0.60

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## Types of data visualisation

### Data tables

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000		
<b>Bluetongue disease</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
<b>Brucella</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Cholera</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Diphtheria</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Epidemic typhus</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Scarlet fever</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Shigellosis</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Typhoid</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Whooping cough</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Yersinia pestis</b>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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## Types of data visualisation

### Standard graphs

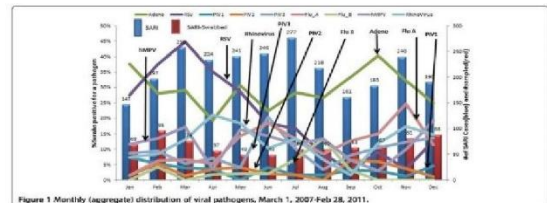
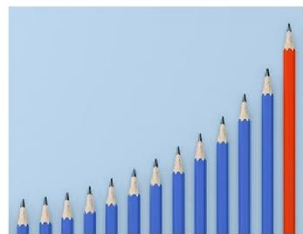


Figure 1 Monthly (aggregate) distribution of viral pathogens, March 1, 2007-Feb 28, 2011.

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## Types of data visualisation

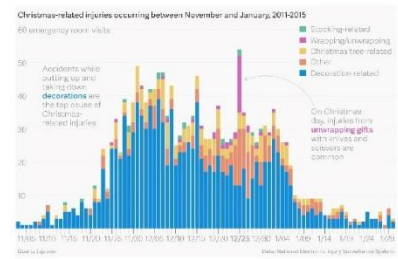
### Themed graphs



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## Types of data visualisation

### Epi curves



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## Types of data visualisation

### Fancy graphics

Types of cancer by age

Age Group

- 18 - 34
- 35 - 49
- 50 - 64
- 65 - 74
- 75 +

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## Types of data visualisation

### Geographic maps

What do you call the object that you might drink water from in a park or school?

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## Types of data visualisation

### Chloropleth maps

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## Types of data visualisation

### Heat maps

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## Types of data visualisation

### Phylogenetic trees

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## Types of data visualisation

### Circular Phylogenetic trees

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## Types of data visualisation

### Social network analysis

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## Types of data visualisation

### Systems analysis

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## Types of data visualisation

### Infographics

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## Types of data visualisation

### Digital dashboards

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## Types of data visualisation

### Word clouds

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## Types of data visualisation

### Polling apps

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## Interactive examples

### Institute for Health Metrics and Evaluation

<https://vizhub.healthdata.org/gbd-compare/>

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## Interactive examples

### Victoria DHHS Notifiable Conditions

<https://www2.health.vic.gov.au/public-health/infectious-diseases/infectious-diseases-surveillance/interactive-infectious-disease-reports/state-wide-surveillance-report>

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## Interactive examples

### Gapminder

[https://www.gapminder.org/tools/#\\$state\\$time\\$value=1814;:&chart-type=bubbles](https://www.gapminder.org/tools/#$state$time$value=1814;:&chart-type=bubbles)

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## Interactive examples

### Fitbit

<https://www.fitbit.com>

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## Good

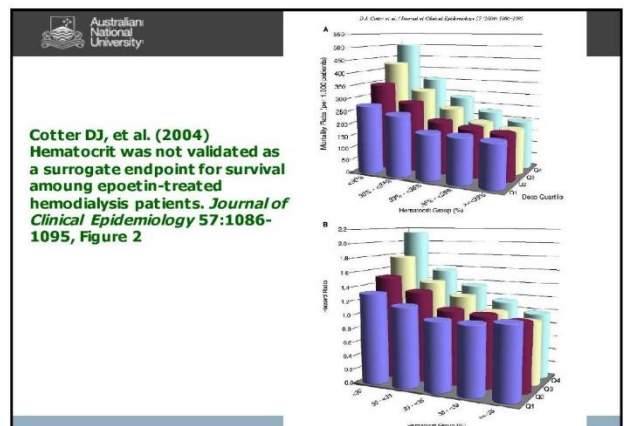
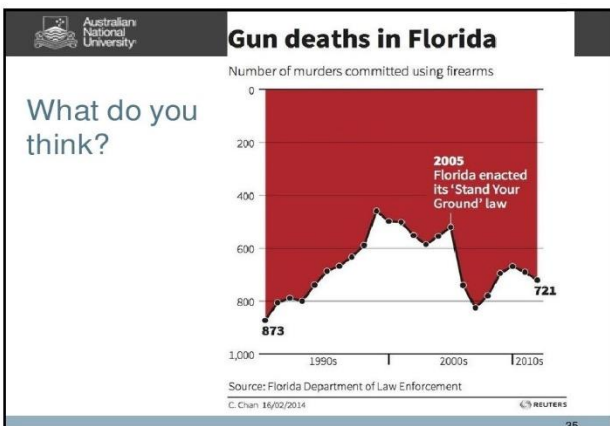
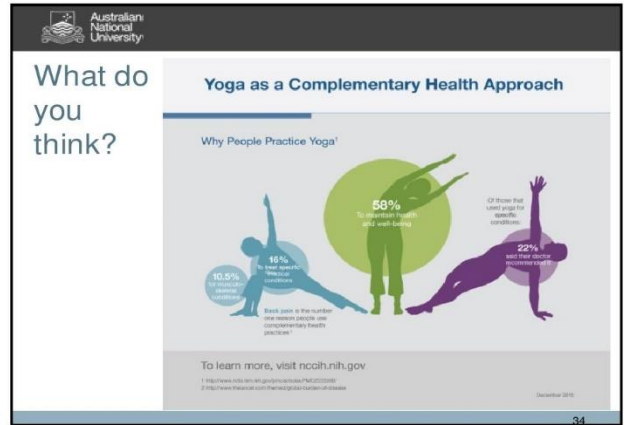
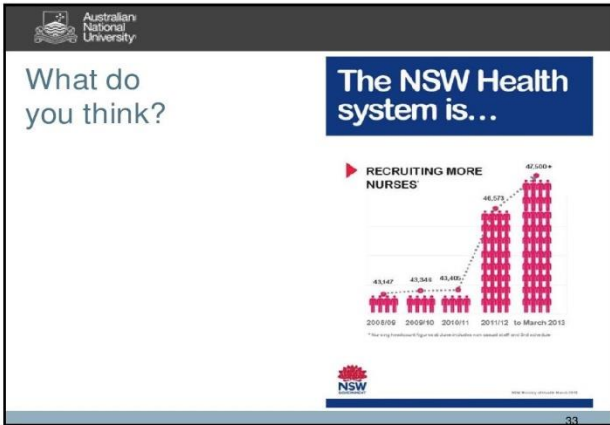
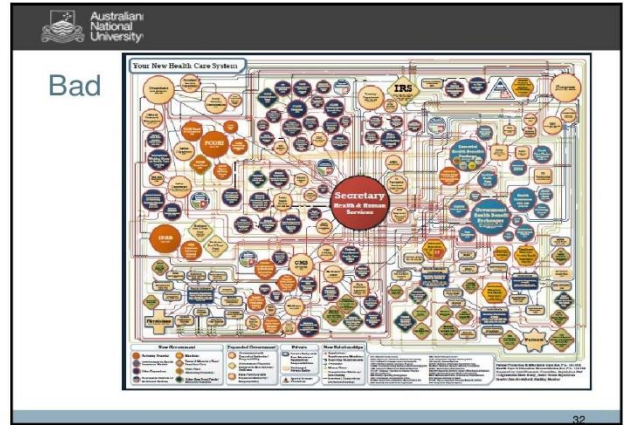
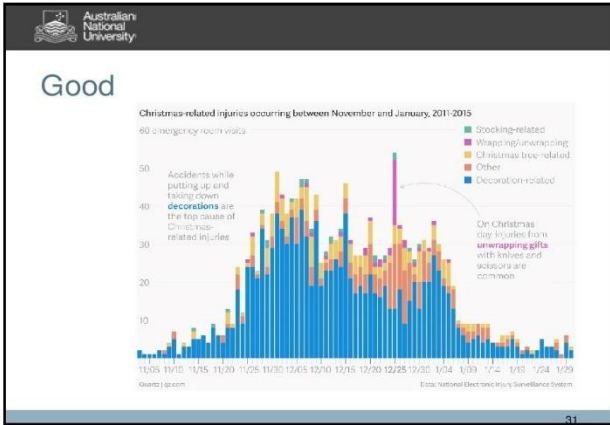
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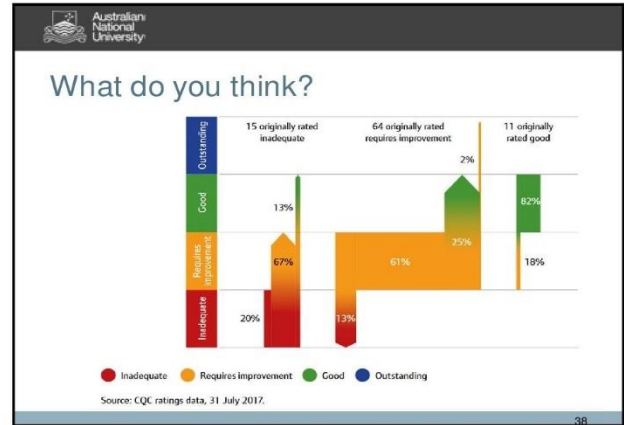
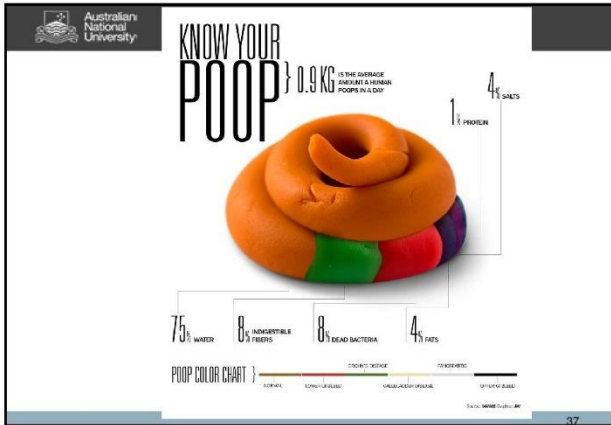
## Bad

Figure 1 Monthly (aggregate) distribution of viral pathogens, March 1, 2007-Feb 28, 2011.

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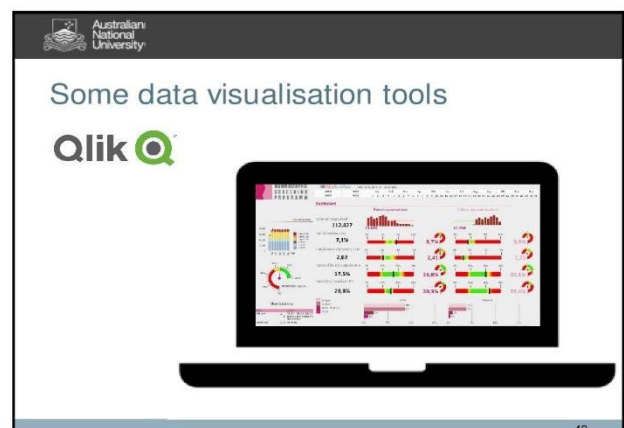
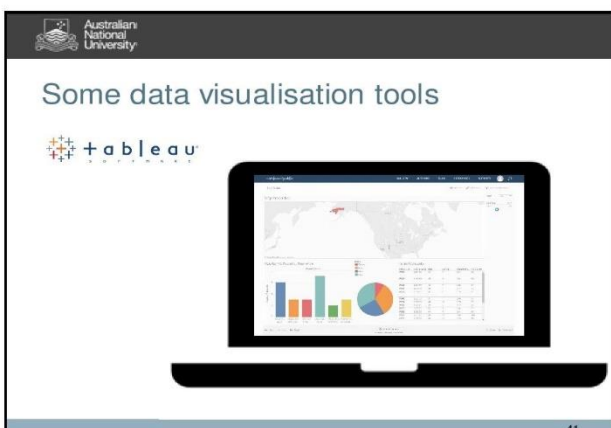






- ### Why visualise data?
- To Communicate data
  - To identify trends e.g. geographic distribution, phylogenetic relationships
  - To enhance detection of patterns
  - To Identify outliers

- ### Interactive data visualisation tools
- Hundreds of products on the market
  - Very few are free
  - Be very mindful of data uploaded
  - Consider where data are hosted and data regulations (or lack of them) in different countries



## Some data visualisation tools

 Power BI



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## Power BI Demo

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## Today

- Hans Rosling
- What is data visualisation
- Types
- Interactive examples
- Why is data visualisation important
- Rate these
- Some data visualisation tools
- Demo
- Principles for presenting data

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## Additional Resources

- Online Courses
  - Coursera: <https://www.coursera.org/courses?query=data%20visualization>
  - ADMA: <https://www.adma.com.au/ig/course/data-visualisation>
  - edX: <https://www.edx.org/learn/data-visualization>
  - Data Camp: <https://www.datacamp.com/courses/topic/data-visualization>
  - Tableau, Qlik and Microsoft all run online courses for their products



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## Lesson from the Field

### Tuberculosis in Australia: Epidemiological challenges in cluster and outbreak investigations

Presented on 17 April 2019

Participants – Stephen Harfield, Anthea Katelaris, Tamara Riley

#### 1. Learning Objectives

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

1. Understand the basics of TB transmission.
2. Understand the common surveillance methods for detecting TB clusters.
3. Define and apply the criteria for declaring a TB cluster/outbreak.
4. Develop a robust cluster/outbreak case definition.
5. Estimate the infectious period for cases.

#### 2. Required Reading

Please read over the introductory material in this document and familiarise yourself with the following two papers (sent along with this lesson):

Dheda K, Barry C, Maartens G. Tuberculosis. *The Lancet*. 2016;387(10024):1211-26 – **this short review article provides a good overview of TB.**

Denholm J, Coulter C, Bastian I. Defining a tuberculosis cluster or outbreak. *Commun Dis Intell Q Rep*. 2016;40(3):E356-e9.

#### 3. Exercises

After completing the required reading, work through **exercises 1, 2 and 3**. Please send your completed exercises to [shaun.coutts@anu.edu.au](mailto:shaun.coutts@anu.edu.au) by **15 April 2019** and we will discuss at the LFF video conference at **3PM on 17 April 2019** (details TBA).

#### 4. Tuberculosis – a (very) brief overview

Tuberculosis (TB) in humans is caused by infection with one of the bacteria in the *Mycobacterium tuberculosis* complex (MTC). Most TB cases are caused by *Mycobacterium tuberculosis*. Other mycobacteria in the MTC that can cause tuberculosis in humans include *M. bovis* and *M. africanum*.

A person with infectious TB disease (e.g. pulmonary or laryngeal TB) can forcefully expel *M. tuberculosis* in droplet nuclei when they cough, sneeze, speak or sing. Droplet nuclei can remain



suspended in the air for extended periods, depending on the environment. Transmission can occur when another person inhales these droplet nuclei into their lungs.

Four key factors influence whether a person exposed to an infectious TB case will become infected:

1. The infectiousness of the case (e.g. a case with untreated pulmonary TB is highly infectious).
2. The susceptibility of the exposed individual (immune status due to age, comorbidities etc.).
3. The duration, frequency and nature of the exposure (frequent prolonged exposure increases the risk).
4. The environment in which exposure occurred (infection is more likely to occur in closed environments).

Once infection begins, the immune system in most people can control and contain the TB bacteria, although it may have already spread to other parts of the body via the lymphatic system. These people are said to have latent TB infection (LTBI) and are not considered TB cases.

People with LTBI are not infectious but may later develop active TB disease and become infectious. This may occur after a short period, or years to decades after their initial exposure and infection. This variable latency period is one of the things that makes TB outbreak investigation challenging.

TB is a notifiable disease in all Australian states and territories. Confirmed cases are notified to health authorities based on the following CDNA case definition, which requires either laboratory definitive OR clinical evidence:<sup>1</sup>

#### **Laboratory definitive evidence**

1. Isolation of *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis* or *M. africanum*, excluding *M. bovis* var BCG) by culture.

OR

2. Detection of *M. tuberculosis* complex by nucleic acid testing EXCEPT where this is likely to be due to previously treated or inactive disease.

#### **Clinical evidence**

1. A clinician experienced in tuberculosis makes a clinical diagnosis of tuberculosis, including clinical follow-up assessment to ensure a consistent clinical course.

## 5. Detecting TB clusters

TB clusters are primarily detected by one or more of the following methods:<sup>2</sup>

**Case-based surveillance** - the detection of an increase in cases (beyond what would normally be expected) in a geographic area, community or demographic group over a certain period. This may occur at the surveillance level (e.g. identified by a TB epidemiologist) or at the frontline (e.g. identified by TB nurses or clinicians in the community).

**Genomic surveillance** – in Australian health departments and public health laboratories the two most commonly used methods on TB clinical isolates for genomic surveillance are the mycobacterial interspersed repetitive unit-variable number tandem repeat typing scheme (MIRU-VNTR) and whole genome sequencing (WGS). These methods identify closely related isolates and can prompt further investigation of links between genomically-related cases that may not have been apparent based on other surveillance data. Both methods require a culture from a clinical specimen – this is not always available for every case.

**TB contact investigations** - Contact investigations are undertaken to identify people exposed to an infectious TB case, to assess them for infection, and to provide treatment as appropriate. Contacts are prioritised for investigation based on their risk of infection. Contact investigation may identify newly infected persons (i.e. infected by the case that prompted the investigation) or identify a possible source case.

## 6. Defining TB clusters and outbreaks

In Australia, the definitions for TB clusters and outbreaks have been defined in a policy paper by the National Tuberculosis Advisory Committee (NTAC) as follows:<sup>3</sup>

<b>Cluster</b> - 2 or more active cases with <b>identified epidemiological links</b> and the <b>same genotype</b> as defined by the method used.
<b>Probable cluster</b> - 2 or more active cases with <b>identified epidemiological links</b> where <b>genotyping is not feasible</b> or the <b>genetic variability between isolates recovered from cases is minimal</b> , defined as no more than 1 locus variance for MIRU-typing or as advised by expert analysis for WGS.
<b>Possible cluster</b> - 2 or more active cases with the <b>same genotype</b> as defined by the method used where <b>temporal and geospatial association is plausible</b> but <b>no direct epidemiological link is identified</b> .
<b>Outbreak</b> - a <b>cluster</b> that includes <b>3 or more active cases</b> with <b>evidence of serial transmission</b> (i.e. two or more of the cases have transmitted disease)

The **index case** is the first case identified in cluster or outbreak. This may be different to a **source case**; a person identified as being responsible for transmitting TB to the other cases in the cluster or outbreak.

## 7. Developing a TB cluster case definition

As with any cluster or outbreak investigation, it is important to develop robust case definitions. TB cluster and outbreak case definitions usually include the following elements:

1. Information about the location or **place** (e.g. geographic area – could be broad like a state or city or narrow like a boarding house or workplace).
2. Characteristics about the affected **persons** (e.g. demographic characteristics, activities, behaviours, lifestyle, community).
3. Information about the **time** during which the outbreak occurred (usually start of the infectious period if there is a suspected source case or may go back further if this is unknown).
4. TB **genotype** information if available.

The person, place and time elements are often categorised together as “**epi links**”.

As it is not always possible to assemble all elements for each case (at least not immediately), cases are often further classified into “**Possible**”, “**Probable**” and “**Definite**” cases.

## 8. Estimating the infectious period for a cluster/outbreak case

Due to the nature and course of TB disease, it is often impossible to determine the start of a case’s infectious period.

Key clinical details can be used to estimate the infectious period. These are approximate date of symptoms onset and diagnosis, sputum smear results (smear positive cases are generally highly infectious) and radiographic results (the presence of lung cavities suggests prolonged illness and infectiousness).

The US CDC recommends the following guideline for the estimation of infectious periods, based on expert opinion.<sup>4</sup> This guideline suggests that (generally) a case’s infectious period can be estimated to end after two weeks of appropriate treatment.

<b>TB Symptoms</b>	<b>Sputum Smear Positive</b>	<b>Cavitary Chest Radiograph</b>	<b>Recommended start of infectious period</b>
Yes	No	No	3 months before symptom onset or first positive finding consistent with TB disease (whichever is longer)
Yes	Yes	Yes	3 months before symptom onset or first positive finding consistent with TB disease (whichever is longer)
No	No	No	4 weeks before date of diagnosis
No	Yes	Yes	3 weeks before first positive finding consistent with TB disease

## 9. References

1. Australian Government Department of Health. Tuberculosis case definition Canberra: Australian Government; 2011. Available from: [http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd\\_tb.htm](http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_tb.htm).
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3. Denholm J, Coulter C, Bastian I. Defining a tuberculosis cluster or outbreak. Commun Dis Intell Q Rep. 2016;40(3):E356-e9.
4. Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2005;54(Rr-15):1-47.

## Task 1. Cluster / Outbreak Definition

Having read the NTAC definitions, for each of these scenarios consider:

1. *Would you classify it as a cluster? Probable cluster? Possible cluster?*
2. *An outbreak?*
3. *Why or why not? What other information would be useful?*
4. *What challenges have you noticed in classifying these scenarios?*
5. *Do you think it is important to differentiate a TB cluster from a TB outbreak?*

### **Scenario 1.**

A six-year-old child is diagnosed with TB of the lymph nodes at a hospital in inner-metropolitan Melbourne. No clinical isolate is available from the child for genotyping.

The TB team investigate the household contacts of the case. They find:

- The case's father and teenage sister have latent TB infections.
- The case's stepmother refuses to provide a specimen or be tested, but the father reports that she has been coughing for at least two months and appears to have lost some weight.

### **Scenario 2.**

Janice is a 2-month-old child who has been clinically diagnosed with pulmonary TB in rural Tasmania. This area of Tasmania normally reports less than one case of TB per year on average.

Contact investigation by the TB team find that Janice's uncle Barry also has active pulmonary TB disease. He normally lives in WA but is in between jobs so has been living with the family in Tasmania for the past five months, working on perfecting his home-brew recipes. He is more than happy to produce a sputum specimen for culture and sequencing.

As an infant, Janice is unable to produce sputum, so no culture is available for genotyping.

### **Scenario 3.**

Harry, a 32-year-old Vietnam-born man, is diagnosed with active pulmonary TB in Sydney. Following a contact investigation of his household contacts, his three-year-old son is also found to have active TB disease.

Harry's employer, SuperCon Semiconductors Pty Ltd, contacts the TB team. Harry has told them he has TB and they are worried that he may have exposed his co-workers. They report that Harry usually works in a small enclosed room assembling semiconductors along with nine colleagues. The TB team decide to conduct a screening session at the workplace.

Six of Harry’s colleagues agree to be screened for TB. The other three aren’t too fussed and just want to see how things pan out. Screening results show one of Harry’s colleagues, Boris, has active TB. The rest are negative.

Specimens are obtained for culture and WGS from all active cases – they are indistinguishable on WGS. With these results in hand, the TB epi searches the surveillance database for other cases with the same sequence – there is one case from two months ago, a 26-year-old dentist who practices at Bright White Dental Clinic in the same suburb as Supercon Semiconductors.

The TB team ask the two workplace cases when they last visited a dentist. Harry hasn’t been to the dentist in at least 12 years. Boris recently had a gold crown fitted at Bright White Dental Clinic but can’t recall the dentist’s name.

## Task 2. Cluster Case Definition

Bayside Public Health Unit’s TB team have asked you, as a respected MAE Scholar, to assist in a suspected TB outbreak investigation as their regular TB epi has taken some unexpected leave.

Sorting through the sheets of paper on the epi’s desk, you find they have drafted up an outbreak case definition:

- A **definite case** is defined as a TB case notified to Bayside Public Health Unit from 1 January 2017, meeting the national confirmed TB case definition, who was epidemiologically linked to other cases within the outbreak and had a genomic profile matching the outbreak strain.
- A **probable case** meets the criteria for a definite case but has an unknown genomic profile.
- A **possible case** meets the criteria for a definite case but has no established epidemiological link to another case in the outbreak.

The only other information you can find on the desk is that the outbreak genotype is believed to be GT101.

ID	Date Notified	Classification	Age	Gender	Genotype	Case notes
1	10/10/2018		17	F	GT101	Year 12 student at Bayside Grammar School. Failing chemistry.
2	08/05/2018		23	F	GT101	Science student at Bayside University. Lives in a share house.
3	07/02/2018		21	M	GT101	Unable to contact case.

4	22/07/2018		55	F	Pending	Manager at Bayside UniHouse at Bayside Uni.
5	09/01/2018		23	M	GT101	Arts student at Bayside University. Lives at Bayside UniHouse.
6	07/08/2019		28	F	GT473	PhD student at Bayside University. Lives off-campus.
7	25/12/2018		33	F	Pending	MPH student at Bayside University. Lives off-campus.
8	22/01/2019		1	F	N/A	Child of case #7.
9	15/11/2016		62	M	Pending	Maintenance worker for Bayside UniHouse. Collects stamps.

1. Looking at the available information, what would you consider valid “epi links” for this investigation?

2. Classify the eleven cases in the line list based on your case definition.

3. What other information would be useful in classifying the cases?

### Task 3. Estimating Infectious Periods

Based on the information in section 8, estimate the infectious period for the following cases.

Assume the first positive finding consistent TB disease is the same as the date diagnosed.

ID	Date Diagnosed	TB Symptoms	Smear Positive	Cavitary CXR	Symptom Onset	Treatment Start Date	Infectious Start	Infectious End
1	08/10/2018	No	No	No	?	10/10/2018		
2	08/05/2018	Yes	Yes	Yes	02/04/2018	10/05/2018		
3	01/02/2018	No	Yes	Yes	?	10/02/2018		
4	21/07/2018	Yes	No	No	19/03/2018	25/07/2018		
5	07/01/2018	No	No	No	?	09/01/2018		

1. What other considerations might alter your estimation for the start of a case’s infectious period?

2. What about the end of a cases’ infectious period?



# Social Network Analysis

## An Introduction to the Basics

Shaun Coutts

### What are social networks?

A set of relationships linking individuals, entities, places or events.



### What is social network analysis?

A strategy (or set of methods) for investigating, describing and visualising social structures based on network and graph theory.

Based on the relationships between individuals or entities.

### How is it useful in applied epi?

Visualising network structures and dynamics.

Describing network properties.

Linking these structures and properties to disease transmission (w/ the right non-SN data).

### Network terminology

**Nodes** (aka vertices, actors)

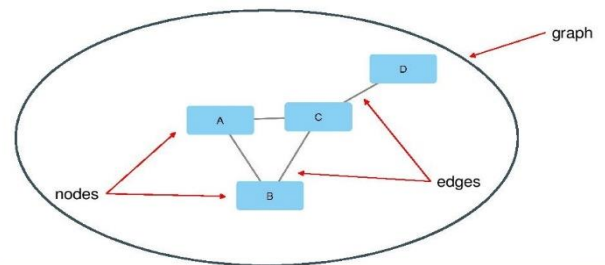
- may be people, animals, places...

**Edges** (aka arcs, ties)

- may be relationships, affiliations, interactions...
- may have weightings.

**Graph**

- a set of nodes and edges forming a social network.



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Bridge = an edge where removal creates two separate networks

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Cutpoint = a node where removal creates two separate networks

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### Storing network data

- Edge list
- Adjacency matrix
- Both easily created in Excel

Source	Target
A	B
A	C
B	C
C	D

	A	B	C	D
A	0	1	1	0
B	1	0	1	0
C	1	1	0	1
D	0	0	1	0

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### Directed vs Undirected networks

- Directed networks – edges connect in particular direction. e.g.  $A > B$  but not  $B > A$
- Undirected networks – edges connect both ways.

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### The ANU Social Network

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Australian National University

### Edge list

Source	Target
Colleen	Shaun
Colleen	Brady
Emma	Shaun
Shaun	Sophie
Shaun	Brady
Emma	Sophie
Emma	Caroline
Caroline	Shaun
Caroline	Sophie
Caroline	Brady
Emma	Colleen
Brady	Sophie

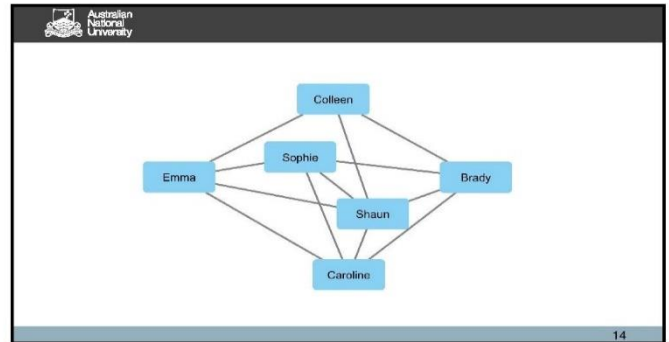
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### Adjacency Matrix

	Brady	Caroline	Colleen	Emma	Shaun	Sophie
Brady	0	1	1	0	1	1
Caroline	1	0	0	1	1	1
Colleen	1	0	0	1	1	0
Emma	0	1	1	0	1	1
Shaun	1	1	1	1	0	1
Sophie	1	1	0	1	1	0

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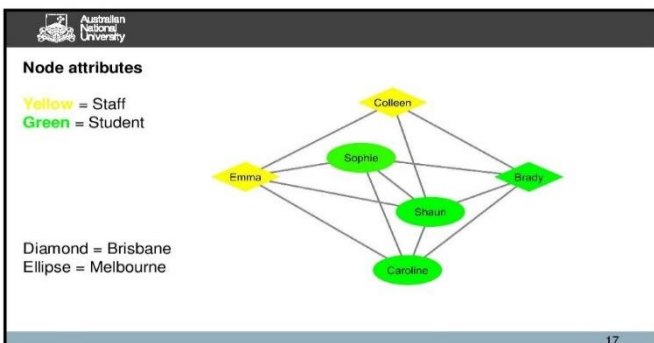
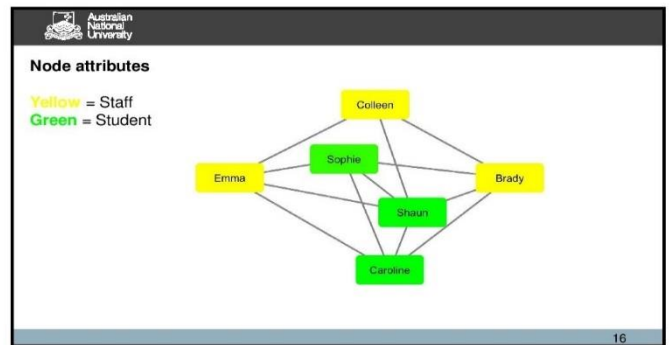


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### Adding network attributes

Node attributes  
e.g. individual's role at ANU, located of work

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### Adding network attributes

Edge attributes  
– e.g. the nature of social connection/relationship between individuals.

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### Edge list

Source	Interaction	Target
Colleen	Supervisory	Shaun
Colleen	Supervisory	Brady
Emma	Supervisory	Shaun
Shaun	Cohort	Sophie
Shaun	Cohort	Brady
Emma	Supervisory	Sophie
Emma	Supervisory	Caroline
Caroline	Cohort	Shaun
Caroline	Cohort	Sophie
Caroline	Cohort	Brady
Emma	Colleague	Colleen
Brady	Cohort	Sophie

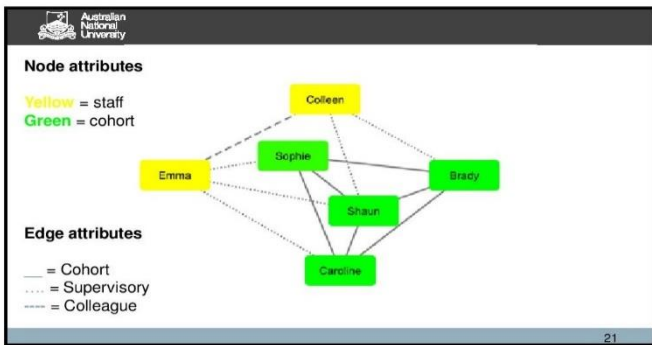
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### Adjacency Matrix

	Brady	Caroline	Colleen	Emma	Shaun	Sophie
Brady	-	Cohort	Supervisory	-	Cohort	Cohort
Caroline	Cohort	-	-	Supervisory	Cohort	Cohort
Colleen	Supervisory	-	-	Staff	Supervisory	-
Emma	-	Supervisory	Colleague	-	Supervisory	Supervisory
Shaun	Cohort	Cohort	Supervisory	Supervisory	-	Cohort
Sophie	Cohort	Cohort	-	Supervisory	Cohort	-

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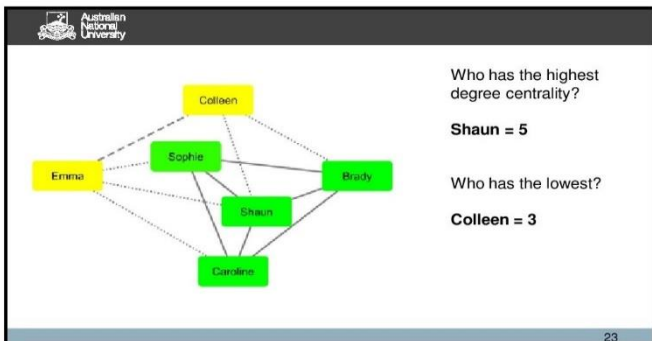
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### Network metrics

#### Degree centrality

- Simplest measure of the connectivity of an individual node within a social network.
- Measures the number of connections between a node and all other nodes in the network.

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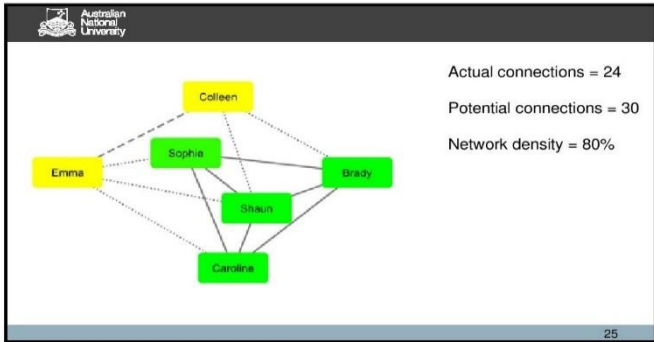
### Network metrics

#### Network density

Actual number of connections in network / Potential number of connections in network

Index of the overall connectedness within a network.

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*Denser networks are an indication of higher contact rates among people, which may create more opportunities for transmission*

- Doherty et al. 2005

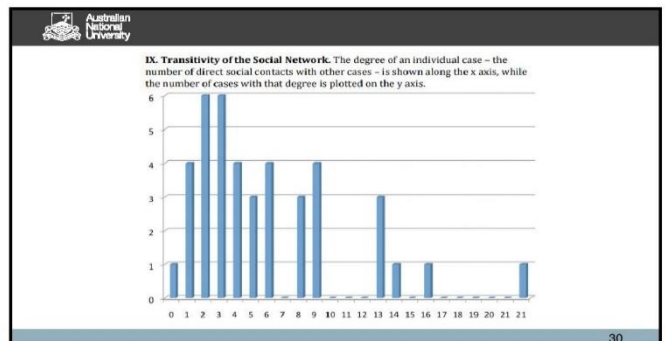
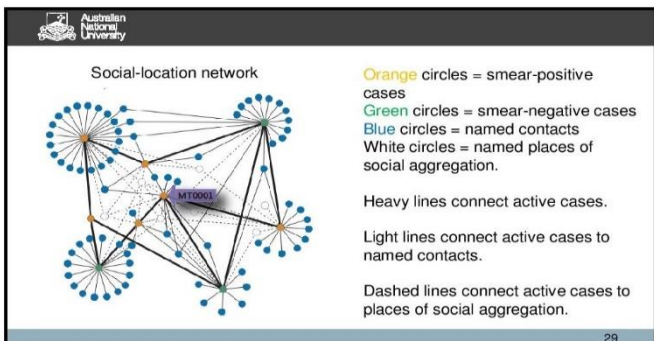
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

**Whole-Genome Sequencing and Social-Network Analysis of a Tuberculosis Outbreak**

Jennifer L. Gardy, Ph.D., James C. Johnston, M.D., Shannan J. Ho Sui, Ph.D., Victoria J. Cook, M.D., Lena Shah, M.Sc., Elizabeth Brodtkin, M.D., Shirley Rempel, R.N., Richard Moore, Ph.D., Yongjun Zhao, D.V.M., Robert Holt, Ph.D., Richard Varhol, M.Sc., Inanc Birol, Ph.D., Marcus Lem, M.D., Meenu K. Sharma, Ph.D., Kevin Elwood, M.D., Steven J.M. Jones, Ph.D., Fiona S.L. Brinkman, Ph.D., Robert C. Brunham, M.D., and Patrick Tang, M.D., Ph.D.

- An outbreak of tuberculosis over a 3-year period in British Columbia, Canada.
- Traditional contact tracing did not identify a plausible source.
- Used a detailed social-location network questionnaire and analysis, combined with WGS.



- Suspected source case was connected to all but two early cases through direct contact or a shared social setting. (i.e. high degree centrality).
- Each cases reported social contact with average of six other cases (high network density).
- Use of the SNQ improved case-finding by revealing previously unreported social interactions, and identified locations frequented by infectious cases (hotels, meal centers, community centers, crack houses).

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## Conclusion

- Networks matter.
- Whole suite of analysis methods and metrics available.
- Choose those that suit your study/data.
- Interpret in the context of other data (spatial/temporal etc.)

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## Software for social network analysis



Cytoscape



Gephi



R (with the iGraph package)

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## Further resources

<https://www.datacamp.com/courses/network-analysis-in-r>



Yang et al.  
Social Network Analysis: Methods and Examples



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## Appendix C

### SaMELFS Samoa Mosquito Survey and Molecular Xenomonitoring Study

This appendix contains a short report on my experience in Samoa as a team leader/epidemiologist for the SaMELFS Samoa mosquito survey and molecular xenomonitoring study between 14 June 2019 and 30 June 2019, and a copy of an online news article I was invited to write for publication on the ANU Research School of Population Health and MAE program websites.

## Background

Lymphatic filariasis (LF) is mosquito-borne neglected tropical disease caused by filarial worms. In 1997 the World Health Organization called for the global elimination of LF as a public health problem by 2020, using a strategy of annual mass drug administration (MDA) - single dose diethylcarbamazine (DEC) plus albendazole for the entire at-risk population. In 2017, following safety and efficacy trials, the WHO endorsed the addition of ivermectin to the MDA regimen (triple drug MDA with ivermectin, DEC and albendazole, (IDA)) for countries that have ongoing transmission despite implementing the recommended rounds of MDA. Despite significant progress toward the elimination goal in some countries, it will not be achieved globally by 2020.

*Wuchereria bancrofti* is the causative parasite of LF in Samoa, with *Aedes polynesiensis* as the primary vector. Despite completing multiple rounds of MDA in the past, recent surveillance indicated ongoing transmission. Samoa completed a first round of IDA in August 2018, with a second round scheduled for December 2019.

Surveillance and Monitoring to Eliminate Lymphatic Filariasis and Scabies from Samoa (SaMELFS Samoa) is an ANU-led project that aims to develop a monitoring and evaluation strategy that can be used in Samoa to determine when the risk of LF transmission has been sufficiently reduced to stop IDA with little to no risk of transmission resurgence. The principal investigators for SaMELFS Samoa are Colleen Lau (ANU), Sarah Sheridan (University of New South Wales), Patricia Graves (James Cook University) and Robert Thomsen (Samoa Ministry of Health). SaMELFS Samoa is funded by the Task Force for Global Health (USA) and the Bill and Melinda Gates Foundation.

The two main components of SaMELFS Samoa are a human seroprevalence study and a mosquito survey/molecular xenomonitoring study. The primary aims of the mosquito survey are to investigate associations between the presence of PCR-positive mosquitoes and the seroprevalence of LF in humans, and to assess the usefulness of molecular xenomonitoring (MX) as an early and sensitive indicator of LF transmission.

## Role

I was offered the opportunity to work as a team leader for the SaMELFS Samoa Mosquito Survey from 14-30 June 2019 through my academic supervisor Associate Professor Colleen Lau and MAE colleague Brady McPherson (Australian Defence Force Malaria and Infectious Disease Institute). I had previously worked with several of the SaMELFS Samoa investigators in 2017 to publish a paper on LF in American Samoa based on secondary data, so I was keen to gain some first-hand field experience in an LF surveillance and elimination program.

During my time in-country the SaMELFS Samoa Mosquito Survey team generally consisted of myself (team leader/epidemiologist), two entomologists, and three Samoan Red Cross staff. We were based at a hotel in Apia, where the team had established a small entomology field laboratory and office.

MX was conducted at a total of 35 primary sampling units (PSUs) during the survey which consisted of one or two villages, depending on village size. Mosquito trapping at the 14 PSUs was completed during my time in-country. In each PSU, 15 households were sampled using Google Earth. Two teams (consisting of an Australian and a Samoan team member) operated simultaneously in different PSUs, using printed maps and smartphones to locate sampled households. If a household was unoccupied, or was not a household, it was replaced with the next-closest household. Biogents Sentinel mosquito traps (BG traps), baited with BG-Lures, were set at each household for a 48-hour period. The traps were checked, and the battery and catch net changed, after 24 hours.

On a practical level, this meant that every second day we would collect second catches from traps in one village and relocate the traps to a new village on the same day. As we were unable to set or check traps in villages on Sundays due to cultural considerations, traps had to be set as early as possible on a Saturday morning, checked and battery-swapped as late as possible on Saturday afternoon/evening (first catch) and then checked and collected (second catch) as early as possible on Monday morning.

Each catch net (two from each trap over the 48-hour period) was sorted in the lab by the entomologists. All male mosquitoes and other insects were discarded. The remaining female mosquitoes were sorted into the following categories:

- *Aedes polynesiensis*
- *Aedes aegypti*
- *Aedes albopictus*
- *Aedes upolensis*
- *Aedes (Finlaya) spp.*
- *Aedes spp. (other)*
- *Culex quinquefasciatus*
- *Culex spp. (other)*
- Other

Sorted mosquitoes were subsequently pooled into tubes of  $\leq 25$  mosquitoes of the same species from the same household location, dehydrated in an oven to prevent deterioration and packed for shipment to Smith College, USA for PCR testing.

All data collected during the survey were entered directly into the Secure Data Kit (SDK) smartphone app in the field and the lab, using a separate electronic data collection form for each step – setting, sorting and pooling. Data were automatically uploaded from the smartphones onto the secure SDK cloud-based database. I regularly checked the data on the SDK database for errors and inconsistencies using an R script, correcting these using the web-based SDK interface as necessary. Weekly progress reports were compiled weekly and emailed to the principal investigators.

As a team leader for the survey I was also responsible for the day-to-day management of the project, ensuring that village visits, finances, vehicles, accommodation, consumables and other logistics were organised.

## Lessons

My time with the SAMELFS-Samoa study was a valuable experience in conducting operational research in the field. It was also a great introduction to the day-to-day management of a field project in another country – from organising our consumables, to the payment of Samoan staff and undertaking protracted negotiations over the cost of rental vehicle repairs. This all had to be done while respecting the context and customs of the country in which we were working.

Although I had some experience in mosquito trapping and the use of BG traps in Victoria, it was useful to learn more about the ideal positioning of traps, taking into consideration the tropical weather, accessibility for subsequent collections and dangers to the trap (primarily, curious local children and village dogs).

Despite the SDK smartphone-based electronic data management system massively reducing the amount of paper-based data recording, entry and errors in the field, there is still always the possibility (or inevitability) that somebody will enter the wrong number or press the wrong option. The importance of good data management in the field became clear as I ran the regular data checks – it was obviously much easier and preferable to pick up minor human errors in trap numbers, locations, species counts and so forth while the data were fresh than to have to deal with the errors in a dataset when preparing for an analysis.

Importantly I managed to learn a bit about the nation of Samoa, including a few useful words of Samoan. I couldn't think of a better place for my first overseas field epidemiology experience - it is a beautiful country full of welcoming people, to which I would love to return in the future.

## Implications

The results of this mosquito survey and xenomonitoring study will be used to inform the refinement of LF surveillance and monitoring methods in Samoa, elsewhere in the Pacific, and beyond. Colleague from the project will be presenting results from the study at the 2019 Coalition for Operational Research on Neglected Tropical Diseases (COR-NTD) meeting in Washington DC, USA and the 2019 American Society of Tropical Medicine and Hygiene annual meeting in Maryland, USA.

As more countries complete MDA and move toward LF elimination it is increasingly important to have sensitive, validated and cost-effective tools to monitor low-level LF transmission and possible resurgence. Molecular xenomonitoring, if it can be used as a sensitive non-invasive proxy for infection in the human population, may become a key component in the surveillance for LF as endemic countries move toward elimination.

## Acknowledgments

I would like to thank the SaMELFS Samoa team, particularly Colleen Lau and Brady McPherson, for providing me with the opportunity to travel to Samoa for this valuable field experience. Thanks also to my rotating cast of in-country colleagues Stephen Harfield, Christina Neuman, Jess Guidotti, Jo Kizu and Donna MacKenzie for their hard work, patience, commitment and company. Finally, thanks to my Samoan Red Cross colleagues - Nixon, Alesi and Brenda. Without their hard work, local knowledge, diplomacy, navigation skills and great senses of humour the survey wouldn't have been possible.

Online news article written for and published on the ANU Research School of Population Health and MAE program websites.

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## MAE Scholar, Shaun Coutts, on surveillance and monitoring for lymphatic filariasis in Samoa



### Share



### Study

Master of Philosophy (Applied Epidemiology) »

### Contacts

MAE Team

✉ [mae.rsph@anu.edu.au](mailto:mae.rsph@anu.edu.au)

23 JULY 2019

Shaun Coutts is a second year Master of Philosophy in Applied Epidemiology (MAE) scholar at the Australian National University, with a joint field placement between the Burnet Institute and the Victorian Department of Health and Human Services.

In June 2019 Shaun travelled to Samoa as team leader for a mosquito survey, part of the Surveillance and Monitoring to Eliminate Lymphatic Filariasis and Scabies from Samoa study (SaMELFS Samoa).

Shaun's MAE supervisor, ANU's Associate Professor Colleen Lau, is a principal investigator on the study. "The primary aims of the mosquito survey are to investigate associations between the presence of filarial parasites in mosquitoes and in humans at the village level, and to assess the usefulness of this kind of monitoring (known as molecular xenomonitoring) as an early and sensitive indicator of lymphatic filariasis transmission in the community," said Dr. Lau.

Shaun worked alongside Australian entomologists and Samoa Red Cross workers to trap, identify, count and preserve mosquitoes in villages across Samoa, which were then tested for the presence of the filarial parasite that causes lymphatic filariasis - *Wuchereria bancrofti*.

"My involvement with the study in Samoa provided a fantastic opportunity to conduct operational research in the field. Pacific Island nations have made great strides toward eliminating lymphatic filariasis as a public health problem – the outcomes of SaMELFS Samoa study can make a real difference to surveillance and elimination in Samoa and beyond," he said.

MAE scholars have had a strong involvement with the SaMELFS Samoa study; Brady McPherson (Australian Defence Force Malaria and Infectious Disease Institute) is a co-investigator and Stephen Harfield (South Australian Medical Research Institute) worked as a team leader in-country earlier this year. In 2018, Kelley Meder and Gabriela Willis assisted with the human survey, and Julia Maguire with the mosquito survey. MAE alumni Sarah Sheridan and Therese Kearns have also been closely involved as project leaders.

SaMELFS Samoa is funded by the Task Force for Global Health (USA).





