# A Modern Treatise concerning the Plague and the Pox

## Applied Epidemiology of Infectious Diseases in New South Wales

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

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**2021-2023**

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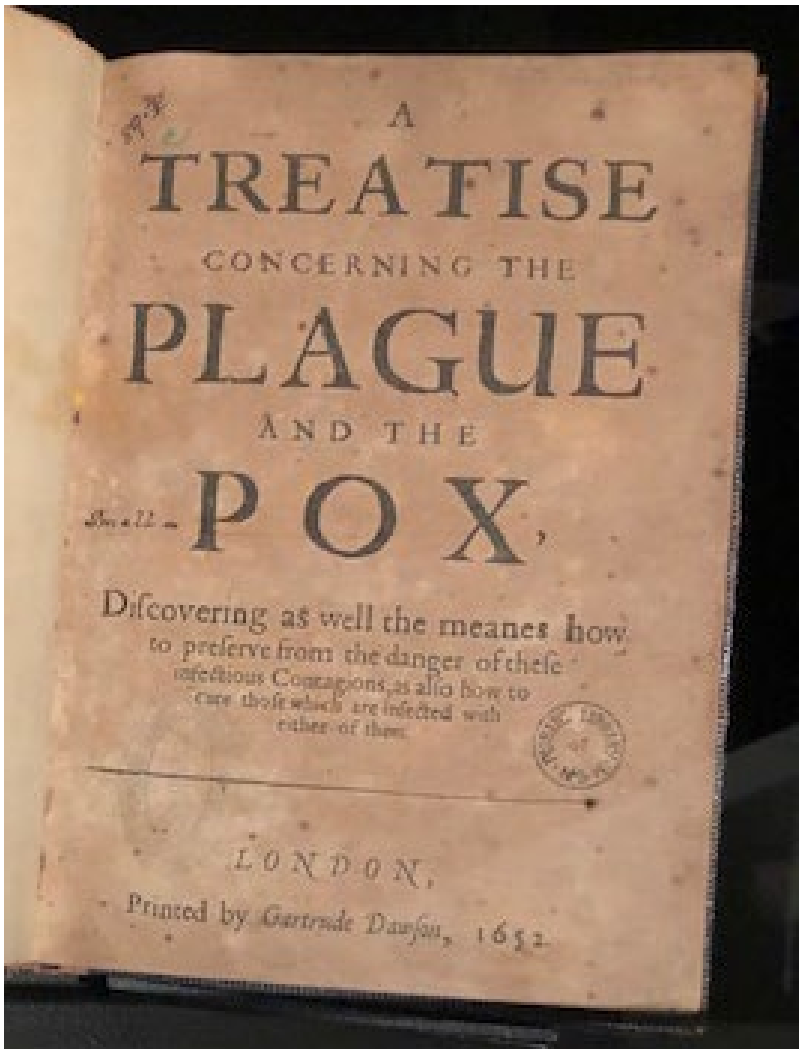

A
TREATISE
CONCERNING THE
PLAGUE
AND THE
POX,
Discovering as well the meanes how
to preserve from the danger of these
infectious Contagions, as also how to
cure those which are infected with
either of them.
LONDON,
Printed by Gertrude Dawson, 1652.

Chapter 1: “The ancient Physicians in times past have greatly doubted, what the essential cause of this disease, which we commonly call the Plague or Pestilence, should be; yet all do agree, that it is a pernicious and contagious Fever, and reckoned to be one of the number of those which are called *Epidemia*, chiefly proceeding of adjusted and melancholy blood, which may be easily perceived, by the extreme heat and inflammation, which inwardly they do feel, that are infected therewith; first assaulting the heart, and astonishing the vital spirits, as also by the exterior Carbunkles and botches which it produceth; whose malignity is such, both in young and old, rich and poor, noble and ignoble, that using all the meanes, which by Art can, or may be devised, yet in some it will in no sort give place, until it hath by death conquered the party infected therewith.”

Edwards. 1652. A treatise concerning the plague and the pox discovering as well the meanes how to preserve from the danger of these infectious contagions, as also how to cure those which are infected with either of them. Oxford Text Archive, Text Creation Partnership, 2004. Available from: http://hdl.handle.net/20.500.12024/A37944

# Originality statement

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

Justine Marshall

15 August 2023

# Acknowledgement of country

I acknowledge the traditional custodians of the lands where I have been privileged to live, work and learn. Sovereignty was never ceded. Health Protection NSW is situated on the lands of the Cammeraygal people, and over the course of the MAE I have lived and worked on the lands of the Cammeraygal and Darramurragal peoples. The Australian National University is on the land of the Ngunnawal and Ngambri peoples, where I have spent many happy weeks learning and growing friendships. I recognise the continued connection of First Nations people to the lands and waters, and I pay my respects to Elders past and present. Always was, and always will be, Aboriginal land.

# Acknowledgements

First thanks go to my supervisors. To Dr Jeremy McAnulty at Health Protection NSW: Veni, vidi, didici. Thanks, JM. Thank you to my academic supervisor at ANU, Dr Md Rezanur Rahaman, for your kindness and support over 2.5 disrupted years. A special thank you to my mentor, Dr Hazel Clothier, for her wisdom, humour, and advice on navigating the MAE and beyond.

I am grateful to the MAEs at NSW Health who welcomed me in strange COVID-19 times: Aurysia Hii, Alicia Arnott, Tracy Tsang, Anny Huang, Anthea Katelaris, Katherine Todd, Hendrik Camphor, and Elenor Kerr. Liz Walker and Kaitlyn Vette arrived late but made up for it with enthusiasm and advice. Special thanks to Katherine, Hendrik, Anthea, Liz, and Elenor for being my supervisors, sage advisors and patient guides on projects and on navigating the MAE in a jurisdictional health department. Endless thanks go to Elenor Kerr, who taught me everything I know about STATA and shared so much of her code.

To my brilliant cohort, MAE21. You made this experience. Each and every one of you has been a delight and you are the most treasured thing I will carry out of this program. From our first days on Zoom to cocktails and karaoke in Canberra, we have bonded together through adversity and bureaucracy, and we have supported, celebrated, and championed each other. We survive and we thrive. The future of epidemiology is in great hands with this network.

To my family and friends, especially my dad, Alan, and my sister, Bryony: thank you for supporting me to do the MAE, even when times were tough.

This thesis is dedicated to my mum, Doreen Marshall (1940-2022). Thank you for growing me, equipping me, and sending me off into the world to live a big life.

# Table of contents

# Abstract

In this thesis I present the body of work I have completed to fulfil the requirements of the Master of Philosophy (Applied Epidemiology) (MAE) at the Australian National University, conducted during my field placement at Health Protection NSW. I present my research projects, teaching activities, and additional field placement activities that together document my experiences as an MAE Scholar and demonstrate the competencies required of the MAE.

I conducted an eight-year retrospective cohort study using routine surveillance data to investigate syphilis reinfections in NSW. Using survival analysis I was able to quantify syphilis reinfections over this period, determine a reinfection incidence rate, and identify factors that predict syphilis reinfection. I evaluated the NSW multidrug resistant organism (MRO) surveillance system, identifying shortcomings in the acceptability and timeliness of the system, and making recommendations for improvement.

I worked on the NSW public health response to the global mpox outbreak in 2022, monitoring the epidemiology of the outbreak in NSW, developing resources including contact factsheets and guidance, and planning for the vaccination rollout. To support the COVID-19 response I conducted data analyses to characterise the arrival of the SARS-CoV-2 Omicron variant in NSW, its spread among the population, and the differences in disease severity between Delta variant and Omicron variant cases. In November 2022 I investigated a foodborne illness outbreak linked to a high tea event at a hotel in the Blue Mountains.

I presented my research on syphilis reinfection and mpox at three national and international conferences in 2022 and 2023, and I prepared a manuscript on the NSW response to the global mpox outbreak for submission to a scientific journal. As part of the MAE teaching requirements, I prepared a lesson from the field for my cohort on neglected tropical diseases, and I co-designed and delivered a group teaching session for the 2022 MAE cohort on antimicrobial resistance and multidrug resistant organism surveillance.

In addition to these projects, I contributed to a range of other activities in Health Protection NSW, including extensive work in the COVID-19 response in 2021 and coordinating and chairing the seminar series *Epi Grand Rounds* in 2022 for the NSW Infectious Disease Network.

# CHAPTER 1

## Introduction and summary of MAE experiences

## Overview of field placements

I commenced as an MAE scholar at the NSW Ministry of Health in St Leonards, Sydney, on 15 February 2021. I was initially placed within the COVID-19 Operations Team in the Public Health Response Branch (PHRB) and spent six months in this team, before moving to the Communicable Diseases Branch (CDB) within Health Protection NSW (HPNSW).

HPNSW is responsible for surveillance and public health response in NSW including monitoring the incidence of notifiable infectious diseases and taking appropriate action to control the spread of diseases. It also provides public health advice and response to environmental issues affecting human health.

When I joined HPNSW there were two main branches, in addition to the Public Health Response Branch (COVID-19): the Communicable Diseases Branch (CDB), which covered areas of immunisation, vaccine preventable diseases, enteric diseases, respiratory and vector-borne diseases, blood-borne viruses and sexually transmitted infections and tuberculosis; and the Environmental Health Branch (EHB), which was sub-divided into the water unit, health risk and regulation unit, and Aboriginal environmental health. Over my time at HPNSW the organisation has undergone a restructure and now has four branches: CDB; the One Health Branch, which now manages zoonotic, enteric, and vector-borne diseases; EHB; and the Epidemiology and Data Systems Branch, responsible for surveillance and data for all of Health Protection NSW.

### Public Health Response Branch

I spent the first six months of my MAE working in the COVID-19 Operations team in the Public Health Response Branch (PHRB). The Ops Team was responsible for providing advice to the executive and other stakeholders on the epidemiological, operational, laboratory and clinical aspects of the pandemic. The team coordinated investigations relating to COVID-19 clusters and outbreaks, especially where there were cross jurisdictional issues. The team investigated high risk COVID-19 cases, such as healthcare workers, or cases where a clear source of infection is not evident.

In this role I was involved in investigating and responding to in-flight transmission and quarantine hotel transmission, public health response to positive cases among flight crews, monitoring outbreaks in other jurisdictions, and observing expert diagnostics panel meetings where complex COVID-19 cases were discussed for discharge from hotel quarantine. I provided public health advice to other areas of government, including the hotel quarantine system, transport, and police. I was also able to learn about the genomics of SARS-CoV-2 and its applications in epidemiology by participating in the weekly whole genome sequencing meetings between the NSW reference laboratory ICPMR, the public health network, and the Ministry.

The Delta outbreak in Sydney that began in June 2021 provided me with an opportunity to participate in cluster investigations, contact tracing and epi linking cases, case interviews, venue risk assessments, and investigating exposures in healthcare, education, and workplace settings. I provided support to Ambulance NSW to develop their capacity to contact trace and risk assess exposures when they had their first COVID-19 positive paramedics in July 2021.

I was also able to observe the response at close quarters and learn a lot about the difficulties in scaling up public health responses, responding to the outbreak in culturally and linguistically diverse communities, and public health messaging. It was amazing to see the public health network in NSW mobilise in response to the outbreak and to learn from that coordination and cooperation.

### Communicable Diseases Branch, Health Protection NSW

In September 2021 I moved to the Communicable Diseases Branch within Health Protection NSW. I supported the CDB Communicable Diseases (CD) on-call response team by managing regular surveillance workflows in the NSW Notifiable Conditions Information Management System (NCIMS), including notifications with unknown condition or unknown/interstate jurisdiction, and event de-duplication. In January 2022 I commenced training to be CD on-call officer, a role that is taken by a member of CDB for a day each week/fortnight, on roster. The CD on-call officer is the focal point for contact between the public health network (PHN), public health units (PHUs), other jurisdictions, and the CDB at the Ministry of Health, and for communication and dissemination both internally and externally.  My first day rostered as CD on-call was 22 February 2022.

## Summary of core requirements

### Design and conduct an epidemiological study

#### Chapter 2: Syphilis reinfection in New South Wales, 2014–2021

Syphilis is a growing health problem, with repeat infections representing a key diagnostic and disease control challenge. In order to quantify and describe syphilis reinfections in NSW, I designed and carried out an epidemiological study. I conducted a retrospective cohort study using infectious syphilis notifications reported in NSW with symptom onset between 01 January 2014 and 02 October 2021. I described the cohort using demographic, clinical and exposure factors, calculated the reinfection incidence rate using negative binomial regression, and used Cox regression models to examine factors associated with reinfection.

During the study period 12% of the cohort experienced repeat notifications, with a reinfection incidence rate of 4.93 per 100 person-years. Factors that predict reinfection include being a male with

same-sex sexual exposure (aHR 2.76) and a having a notification for another sexually transmitted infection (chlamydia or gonorrhoea) in the 12 months prior to first syphilis notification (aHR 5.03). These results can be used to inform the timing and prioritisation of targeted prevention activities. Evidence of prior STIs as a strong predictor of reinfection can be incorporated into screening guidelines, including in antenatal care settings.

## Investigation of an acute public health problem or threat

### Chapter 3: The NSW public health response to the global mpox (monkeypox) outbreak 2022 and a foodborne illness investigation

In May 2022, mpox cases with no travel history to endemic areas of Africa were reported across Europe and North America, and on 18 May 2022 the first case of mpox was notified in NSW. I joined the outbreak response team. My early tasks were to support the Commonwealth Department of Health and Aged Care to draft the mpox national guidelines (SoNG) by conducting rapid literature reviews of the infectious period and symptom profile of mpox, and to draft the NSW factsheets for low-, medium-, and high-risk contacts. As the response developed, I prepared epi summaries, sitreps, and presentation slides for NSW Infectious Diseases Network updates, clinician alerts to GPs and hospitals, and worked on the planning of the vaccination rollout. I have prepared a summary of the epidemiology of the mpox outbreak in NSW and the public health response, for journal publication.

In November and December 2022 I assisted the Nepean Blue Mountains public health unit to investigate a foodborne illness outbreak linked to a high tea event at a hotel. I interviewed cases, established a case definition, described the data by person, place and time, formulated and tested a hypothesis, conducted a cohort study and analyses, and communicated my findings in the form of a report for the PHU and NSWFA. On this occasion the outbreak was self-limited and no control measures were required.

## Evaluate a public health surveillance system or other health information system

### Chapter 4: Evaluation of the Multidrug Resistant Organism (MRO) surveillance system in New South Wales

In February 2019 Health Protection NSW launched a multidrug resistant organism (MRO) surveillance system and made carbapenemase-producing *Enterobacterales* (CPE) infection and colonisation a laboratory notifiable condition. Using the CDC's Updated Guidelines for Evaluating Public Health Surveillance Systems as a framework, I conducted an evaluation of this system. I described the operation of the system, reviewed its performance against its stated objectives, assessed its performance according to a set of key attributes, and made recommendations for improvement. The

evaluation methods included a review of the surveillance data from 2019–2023, and semi-structured interviews with key informants.

### Analysis of a public health dataset

#### Chapter 5: The arrival of Omicron in NSW: Analysis of first cases and comparison with Delta

In December 2021 and January 2022 I supported the COVID-19 team with a series of rapid analyses during the Omicron outbreak. These analyses used surveillance data to characterise the first cases of the Omicron variant of concern (VOC) and compare the demographic, vaccination, and clinical characteristics of Omicron VOC cases to those of Delta VOC cases occurring in the same period. We were able to show that Omicron VOC was responsible for an upsurge in cases in NSW, and that Omicron VOC had replaced Delta VOC as the dominant circulating variant in NSW within 15 days of its introduction into the community.

### Literature review

A targeted literature search and synthesis of relevant information was undertaken for each project. I conducted a literature review to contextualise my syphilis reinfection incidence rate result as part of my epidemiological study, "Syphilis reinfection in New South Wales, 2014–2021." The search strategy I used is detailed in Appendix A of Chapter 2.

### Report to a non-scientific audience

During the mpox outbreak response I prepared clinical alerts for GPs and hospital and sexual health service clinicians, and a factsheet for mpox cases. The clinical alerts were distributed via primary care networks, public health units, and local health districts to clinicians across NSW. The factsheet was provided to mpox cases when they tested positive, to give them information about the infection, their self-isolation period, and how to access help during their illness. The clinical alert and mpox case factsheet are included as appendices to Chapter 3.

I also provided urgent speaking notes for the NSW Minister for Health about mpox on 9 August 2022, which he used to respond to a question from the Member for Sydney regarding NSW Health's work to protect at-risk communities through vaccination.

### Conference or oral presentation

I delivered three oral presentations at conferences during my MAE. On 20 November 2022 I presented "Syphilis reinfection in New South Wales, 2014–2021" at the International Congress on Infectious Diseases in Kuala Lumpur, Malaysia. On 23 November 2022 I gave a poster presentation, "Once more unto the breach: The public health response of an Australian state to the global monkeypox outbreak

2022," at the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), which was held in Stockholm, Sweden, and online. I attended as an online participant. On 20 June 2023 I gave an updated and expanded presentation of "Syphilis reinfection in New South Wales, 2014–2021" at the Communicable Diseases and Immunisation Conference (CDIC) 2023 in Perth, Australia.

I also gave a presentation on mpox and the NSW public health response to the global mpox outbreak to the NSW Infectious Diseases Network on 14 April 2023 as part of their "Bug Breakfast" seminar series.

### Peer-reviewed publication

I prepared the following manuscript as first author:

> Marshall JC, Katelaris A, Wareing H, Rockett R, Gilmour G, *et al*. No evidence of sustained local transmission from imported cases of mpox (monkeypox) linked to global outbreak, New South Wales, Australia, May to December 2022. To be submitted to *Eurosurveillance* August 2023.

### Teaching field epidemiology

I prepared and conducted a 'Lesson from the Field' on neglected tropical diseases and attended lessons delivered by other MAE scholars in my cohort. For the teaching to the first-year scholars in the 2022 cohort, my group prepared and delivered a session on antimicrobial resistance surveillance. These activities are summarised in Chapter 6.

### Coursework

I successfully completed the following coursework subjects of the MAE program:

- POPH8916 Outbreak Investigation
- POPH8917 Public Health Surveillance
- POPH8913 Analysis of Public Health Data
- POPH8915 Research Design and Methods
- POPH8914 Issues in Applied Epidemiology

### Awards

I was awarded an ANU Vice Chancellor's HDR Travel Grant to attend the International Congress on Infectious Diseases in Kuala Lumpur, Malaysia, in November 2022.

## Additional field placement activities

In addition to activities related to the core program requirements, I also took part in the following activities and projects:

- Attended daily CDB "Wrap" meetings to review high priority cases, and any urgent issues in surveillance or the public health network
- Attended weekly CDB surveillance meetings to review data from the NSW Public Health Rapid, Emergency, Disease and Syndromic Surveillance system (PHREDSS), surveillance case counts, highlight current issues or outbreaks in the public health network
- Attended weekly COVID-19 Whole Genome Sequencing meetings
- Attended monthly Infectious Disease Network meetings
- Coordinated and chaired *Epi Grand Rounds*, a monthly epidemiology seminar series, for the NSW Infectious Disease Network in 2022
- Participated in the OzFoodNet Multijurisdictional Outbreak Investigation (MJOI) into *Vibrio parahaemolyticus* detected in oysters from South Australia in November 2021
- Attended an expert panel assessment of multiple human exposures to a confirmed horse with Hendra virus in the Hunter New England LHD (observer)
- Participated in the EpiWATCH workshop, an outbreak simulation exercise with the Biosecurity Program at the Kirby Institute, UNSW
- Worked on CD on-call (Communicable Diseases on-call) team, managing NCIMS surveillance workflows: unknown conditions, unknown jurisdictions, event de-duplication (focus on syphilis), entering lab results and updating surveillance events
- Entered notifications onto the MRO surveillance database, checking notifications, maintaining the MRO surveillance system
- Wrote the MRO Unit handover document in November 2021 to manage staff changeovers, including the standard operating procedure for MRO notifications.
- Responded to correspondence from members of the public to the Minister of Health about the NSW mpox response and vaccination campaign
- Completed the World Health Organisation (WHO) Global Outbreak Alert and Response Network (GOARN) Tier 1 and 1.5 training

- Completed the WHO course “Leadership and programme management in Infection Prevention and Control”
- Completed the WHO course “Introduction to Epidemic Intelligence from Open Sources” (EIOS)

## Summary of MAE requirements

A summary of my projects and activities and how they meet the core MAE requirements is detailed in the table below.

**Table 1: Summary of MAE competencies and core requirements**

| MAE competency | Chapter | | | | |
|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | 6 |
| Investigate an acute public health problem | | ✓ | | | |
| Analyse a public health dataset | | | | ✓ | |
| Evaluate a surveillance system | | | ✓ | | |
| Design and conduct an epidemiological study | ✓ | | | | |
| Literature review | ✓ | | | | |
| Lay summary | | ✓ | | | |
| Conference presentation | ✓ | ✓ | | | |
| Peer-reviewed publication | | ✓ | | | |
| Teaching field epidemiology | | | | | ✓ |

# CHAPTER 2

## Design and conduct an epidemiological study

Syphilis reinfection in New South Wales, 2014–2021

## Chapter 2: Table of contents

## List of abbreviations

| | |
|---|---|
| ABS | Australian Bureau of Statistics |
| AIDS | Acquired Immunodeficiency Syndrome |
| ART / HAART | Antiretroviral therapy / Highly active antiretroviral therapy |
| ASHM | Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine |
| CDB | Communicable Diseases Branch |
| GP | General Practitioner |
| HIV | Human Immunodeficiency Virus |
| HPNSW | Health Protection NSW |
| LHD | Local Health District |
| MoH | Ministry of Health |
| MSM | Men who have sex with men |
| NCIMS | Notifiable Conditions Information Management System |
| NSW | New South Wales |
| PHU | Public Health Unit |
| PrEP | Pre-Exposure Prophylaxis for HIV |
| RPR | Rapid Plasma Reagin test |
| STI | Sexually transmitted infection |
| U = U | Undetectable = Untransmittable |
| VDRL | Venereal Disease Research Laboratory test |

## Preface

This chapter presents my epidemiological study, a retrospective cohort study to quantify reported syphilis reinfections in NSW between 2014 and 2021 and describe their epidemiology, and establish factors associated with syphilis reinfection. This chapter addresses the following competencies:

- Design and conduct an epidemiological study
- Literature review (Appendix A)
- Conference presentation (Appendix B)

## My role

The idea for this project came from Elenor Kerr and Steven Nigro in September 2021. I took the lead role in this project, supervised by Elenor and Steven. From the outline that Elenor gave me, I developed the aims and objectives, research questions, methodology, data collection and analysis plan. I conducted a literature review on syphilis reinfection and incidence rates, and engaged with stakeholders from the initial conception phase all the way to results dissemination. I wrote and secured ethics approval for the protocol, and I obtained and cleaned the data. I conducted the data analysis and wrote up the results.

In April 2022 I presented the draft project to the Communicable Diseases Branch (CDB), the NSW Syphilis Taskforce, and the CDB-Public Health Unit (CDB-PHU) Syphilis Working Group and continued to take part in these meetings throughout 2022. I have worked closely with several Public Health Unit (PHU) colleagues who work on STIs in their communities across NSW and they have provided me with great context and support. In November 2022 I presented the study to the weekly CDB surveillance meeting.

My abstract for this project was successful in competitive selection for an oral presentation at the International Society for Infectious Diseases Congress in Kuala Lumpur, Malaysia, which I delivered in November 2022. A new abstract with additional results on this project was again successful in competitive selection for an oral presentation at the Communicable Diseases and Immunisation Conference in Perth, Australia, 19-21 June 2023. The presentation slides are included in Appendix B.

## Key reflections

This project was my first comprehensive data analysis experience and I learned so much from it. I knew that data analysis would be the most challenging aspect of the MAE for me, but it is the thing I came to learn. For a long time I stood on the sidelines, daunted, unsure how or where to start. In this project, the theory became practice and I picked up the tools. It was a steep but exhilarating learning curve, and I am proud of my new skills.

I learned a lot about the often iterative process of data cleaning, how you often don't realise the cleaning required until you start to examine and manipulate the data, and it doesn't look or behave as expected. The expression 'data cleaning' now has tangible meaning to me.

I also learned about the myriad ways you can and need to re-shape data: from the interim variables you need to create in order to make the actual variable you need, to how and why to reshape a dataset from long to wide.

I grappled with the difficulty of figuring out the many, many small steps in STATA to make everything happen, how to go from "I know what I want" to "I know how to make it." I also learned how to read and interpret STATA outputs to find the answer I was seeking.

I also had a crash course in R to make maps, a skill that I would like to continue to develop. Several colleagues at NSW Health offered me their help in this endeavour and it was fascinating to see how many different approaches and different styles of coding exist for the same task.

I have made a conscious choice in this chapter and throughout my bound volume to use active voice and first person. I have done this to reflect the spirit of the bound volume as a record of my work over the course of the program.

## Public health impact

The global resurgence of syphilis challenges traditional public health approaches to STI prevention. Evidence suggests that individuals with repeat syphilis may represent a core group of transmitters who sustain the epidemic. Policies for prevention need to better consider the role of interventions to decrease rates of repeat diagnoses of sexually transmitted infections.

Time to reinfection for infectious syphilis has never been examined in detail in NSW. This analysis provides the first published calculation of incidence of reinfection in a general population cohort in Australia. It also identifies factors present at first syphilis diagnosis which predict an increased likelihood of reinfection.

This information will help not only to target interventions to groups of people at greater risk of repeat syphilis events, but also demonstrate the value of this methodology and the utility of further research in this area to refine the timing of interventions.

## Acknowledgements

Thank you to Elenor Kerr for being an enthusiastic and supportive guide throughout. Elenor has taken me through every step of this project and has been an excellent supervisor and motivator. Thank you to Steven Nigro for expert biostats advice and for sharing his knowledge of the landscape and recent

history of HIV and STIs in NSW. I am grateful to Jen Pett for teaching me how to make maps in R and for patiently troubleshooting my errors. Thank you to Dr Chris Bourne for guiding me in the clinical aspects of repeat syphilis infections, the challenges of diagnosis and treatment, and for sharing his extensive knowledge and experience of sexual health in NSW. This has been invaluable to me as I came to understand the dataset, the realities of STI prevention and management in NSW, and the practical applications of these study results.

Thank you to Associate Professor Alice Richardson from the Statistical Support Network at ANU for her review of the statistical methodology and advice on building and interpreting the models.

I am grateful to Kwendy Cavanaugh from Sydney LHD and Rachel Latta from Hunter New England LHD for their support and encouragement, for giving feedback at many different points in the development and execution of the project, and for various calls and Teams chats where they patiently allowed me to talk through ideas and gave thoughtful and practical advice in return. The NSW Public Health Network is full of dedicated people like Rachel and Kwendy who bring their considerable knowledge and experience to bear on improving health in NSW.

Thank you to all the staff of Public Health Units in NSW for the work they do every week to review syphilis notifications, lab reports, enter data from enhanced surveillance forms, chase up outstanding surveillance forms, and classify syphilis events correctly. Without their work over many years this dataset would not exist.

And finally, thank you to the CDB-PHU Syphilis Working Group and the Syphilis Taskforce for their guidance over the course of the project.

## Ethics

Ethics approval was granted by the Australian National University Human Research Ethics Committee under protocol 2022/479.

## Abstract

### Background

Syphilis is a growing health problem, with repeat infections representing a key diagnostic and disease control challenge. Reinfections are more likely asymptomatic and thus harder to detect without enhanced screening. Higher reinfection rates have implications for epidemic control and are associated with increased congenital syphilis. Despite this, literature about syphilis reinfection at the population-level is limited. We sought to quantify and describe syphilis reinfections in NSW between 2014 and 2021.

### Methods

NSW infectious syphilis notifications with symptom onset between 01 January 2014 and 02 October 2021 were analysed, with unique person identifiers used to identify single infections and reinfections. We described the cohort using demographic, clinical and exposure factors, reinfection incidence was calculated using negative binomial regression, and Cox regression models examined factors associated with reinfection.

### Results

The cohort comprised 7,975 individuals with an infectious syphilis notification in the study period, with 12% (973/7,975) experiencing repeat notifications (range per person 1–7). The cohort was 92.8% male, 91.3% residents of major metropolitan areas, with median age at first notification 34 years (IQR 28–44). Among males with information available, 85.5% reported same-sex (MSM) exposures.

Among the cohort's 9,171 notifications, 13% (1,196/9,171) were reinfections. The reinfection incidence rate was 4.93 (95% CI 4.61–5.27) per 100 person-years. The median time to reinfection for the whole cohort was greater than eight years. The median time to reinfection for those who became reinfected during the study period was 485 days (IQR 240–901 days). Factors that predict reinfection include MSM exposure (aHR 2.76, 95% CI 2.04–3.74) and a STI notification in the prior 12 months (aHR 5.03, 95% CI 3.00–8.44). Pre-Exposure Prophylaxis for HIV (PrEP) use was not associated with increased risk of reinfection.

### Conclusion

To our knowledge, this is the first study to quantify reinfection at population-level in NSW and indicates that >10% of infectious syphilis notifications are reinfections. The NSW reinfection incidence rate is lower than rates reported in high-risk groups internationally. These results shed light on the contribution of reinfection to the burden of syphilis in NSW and can inform the timing and

prioritisation of targeted prevention activities. In particular, evidence of prior STIs as a strong predictor of reinfection can be incorporated into screening guidelines, including in antenatal care settings.

## Introduction

Syphilis is a sexually transmissible infection caused by the spirochaete bacterium *Treponema pallidum*. The disease causes substantial morbidity and mortality, particularly if it is left untreated and progresses to later stages. The infection can also be passed from mother to foetus during pregnancy, resulting in congenital syphilis, which is associated with serious perinatal consequences including miscarriage, stillbirth and congenital deformities.[1]

Syphilis represents a serious public health threat. Global progress in the control of syphilis has plateaued, with significant increases in syphilis cases seen among men who have sex with men (MSM) since 2000.[2-4] Repeat syphilis infections represent a key diagnostic and disease control challenge, and may represent a core group of transmitters who sustain the epidemic.

Cohort studies have shown that infectious syphilis reinfections are more likely to be asymptomatic.[5-9] In the absence of routine screening there is likely a lower detection rate for reinfections.[10-12] The immunological response to repeat syphilis is also more attenuated than initial syphilis infection.[6, 9]

Higher rates of reinfection have implications for the basic reproduction number (R0), a metric which describes the transmissibility of infectious agents, and epidemic control, by increasing the re-supply of susceptible individuals.[13, 14] Reinfections are also a challenge to the prevention of congenital syphilis, with studies finding between 8.4% and 22.1% of congenital syphilis cases were due to maternal reinfection or treatment failure.[15, 16] Even after successful treatment for syphilis in pregnancy, women can become reinfected, particularly if their sexual partners have not been adequately treated.[1, 16] These women may not be re-tested for syphilis in their pregnancy.

### Syphilis stages and treatment

Syphilis is a complex disease with differing clinical presentations depending on the stage of the infection: primary, secondary, early/late latent, and tertiary. Syphilis is often called “The Great Imitator” as it can easily be mistaken for other illnesses, particularly in the tertiary stage, which complicates diagnosis. At each stage, if the infection remains untreated, it will progress to the next stage.[17]

Syphilis is highly contagious in the first two years after infection, particularly during the primary and secondary stages.[18, 19] This is reflected in the two case definitions for syphilis in NSW: infectious syphilis, less than two years duration (includes primary, secondary and early latent), and syphilis, more than 2 years or unknown duration.[20]

Primary syphilis is characterised by a painless ulcer or sore, called a chancre, at the site of infection. This usually appears between nine and 90 days after infection. The sore may be located on a part of

the body that is hard to see, such as the vagina, anus, or mouth, and be undetected by the case or their sexual partners.[17]

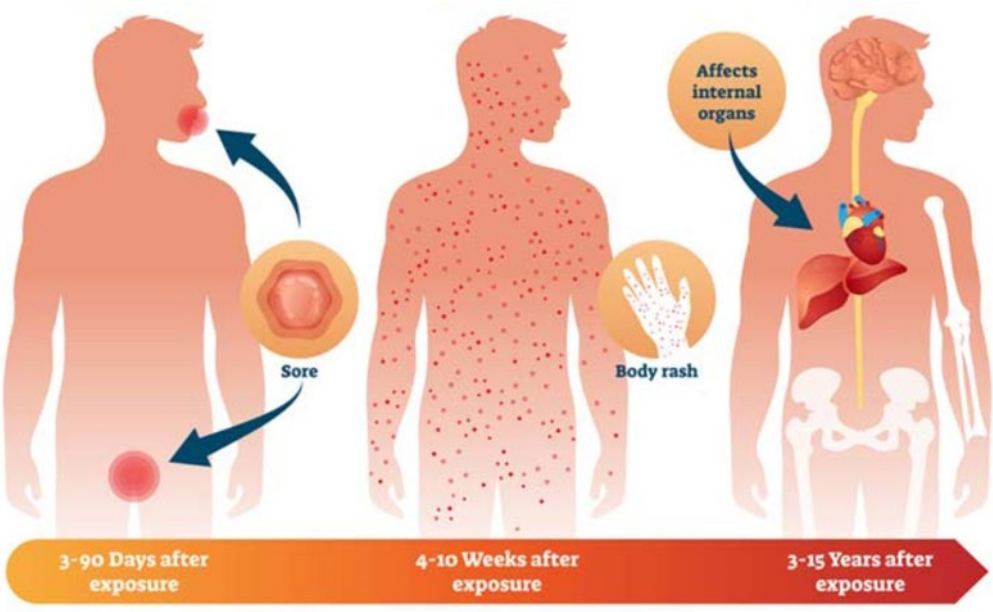
Secondary syphilis typically presents as a rash between four and 10 weeks after infection, which can be present on the palms of the hands and soles of the feet.[21] Most people with secondary syphilis will also have systemic symptoms, such as lymphadenopathy, headache, or fever.[17]

After primary and secondary stages, the disease enters a latent stage that can last up to 30 years. An infected person exhibits no symptoms in this stage.[17]

Tertiary syphilis occurs in 15–30% of untreated cases many years after infection and causes serious damage to various organs depending on the manifestation.[21] Neurosyphilis affects the brain and central nervous system, manifesting as cognitive impairment, dementia, loss of balance or coordination, delusions, seizures and partial paralysis.[21] Cardiovascular syphilis typically causes inflammation of the heart muscle, aortic aneurysms and heart valve disease, which can lead to heart failure.[17] Ocular syphilis and otic syphilis damage the eyes and inner ear respectively, causing vision impairment or blindness, and hearing loss or vertigo.[21]

In NSW, syphilis is usually treated with benzathine penicillin administered by intramuscular injection, with the dosage dependant on the stage of the disease.[17] No immunity is conferred, making reinfection following successful treatment possible, particularly if a person's sexual partners have not been identified, screened, and adequately treated.[22]

Figure 1: Diagram of symptoms across syphilis stages, primary, secondary, and tertiary. Image source: DB Medical [23]



### Congenital syphilis

Vertical transmission of syphilis during pregnancy can lead to serious perinatal consequences such as premature birth, intrauterine growth restriction, miscarriage, stillbirth and perinatal death, as well as serious health problems for any surviving children, such as seizures, and/or permanent damage to a child's brain, teeth, bones, hearing and vision.[1, 24] Transmission from mother to foetus is more likely where the mother has untreated primary or secondary syphilis, making infection during pregnancy a high-risk scenario.[25] Congenital syphilis is completely preventable with appropriate antenatal screening and adequate treatment of infected pregnant people.

### Laboratory diagnosis of syphilis

The diagnosis of syphilis is complex and challenging, due both to ambiguous clinical presentations that mimic other diseases, and the multipart laboratory testing required. Serological tests are the main method of syphilis screening and diagnosis; however, nucleic acid amplification tests such as PCR can be used to detect *Treponema pallidum* in some sites, including chancres in the primary stage of syphilis.[26]

There are two components of syphilis serology, the results of which must be interpreted together. Treponemal-specific tests look for *T. pallidum* antibodies. Once positive (or reactive), individuals generally remain positive for life. These tests do not necessarily indicate active infection. Nontreponemal tests, such as the Rapid Plasma Reagin test (RPR) or Venereal Disease Research Laboratory test (VDRL), detect antibodies produced when cells are damaged by the *T. pallidum* bacteria. Nontreponemal tests are used to track disease activity, including reinfection, and response to treatment by measuring and monitoring the titre over time.[26]

### Trends in syphilis incidence

Syphilis is a growing health problem in NSW and beyond. Globally, in 2016 there were an estimated annual 6.3 million incident cases of syphilis, with a prevalence estimate of 0.5% for both men and women, which increased to 7.1 million in 2020.[27, 28]

Significant global increases in rates of syphilis from 1990 to 2019 have been recorded among males and in high-income countries, with the incidence of syphilis among men who have sex with men (MSM) showing dramatic increases in many countries.[29-32]

As incidence increases, the number of cases in women of reproductive age also rises, together with the risk of congenital syphilis.[1, 33, 34] The United States of America has recorded more than a 5-fold increase in the incidence of primary and secondary syphilis between 2001 and 2019, and a subsequent near tripling of cases of congenital syphilis between 2016 and 2020.[35] Groups of people with poor

access to health care, such as Indigenous women or women experiencing homelessness or drug use, may miss antenatal care, screening, and treatment for syphilis.[1]

In Australia, the infectious syphilis notification rate increased by 63% between 2016 and 2019, from 14.7 to 24.0 notifications per 100,000 population.[36] National increases in infectious syphilis notification have been driven in part by an ongoing multijurisdictional outbreak affecting young Aboriginal and Torres Strait Islander people in remote areas of Queensland, Northern Territory, Western Australia and South Australia that began in 2011.[37] In NSW, crude notification rates for infectious syphilis per 100,000 people increased 65% between 2017 and 2019 (Figure 2).[38-40] Large increases were observed among males and in the 30–39 age group.[40] In August 2016 a change was made to the national case definition for infectious syphilis to include a probable case definition, which resulted in improved reporting of cases. This effect likely accounts for a small part of the increase in notifications observed since 2016.[39]

Figure 2: Crude rate per 100,000 population of Infectious syphilis notifications, NSW, 2017–2021. Figure taken from *NSW Sexually Transmissible Infections Strategy 2022–2026: Data Report, January to December 2021* [40]


Data source: NSW Notifiable Conditions Information Management System (NCIMS) and Australian Bureau of Statistics (ABS) population estimates, NSW Health; data extracted 03 August 2022. Non-NSW residents are excluded. Year is based on calculated onset date.

In 2020 Australia recorded 17 cases of congenital syphilis, the highest annual number since 2001.[41] This followed several years of increasing numbers of infectious syphilis cases among women of reproductive age.[41] NSW has recorded nine cases of congenital syphilis between 2017 and 2021, with a peak of four cases in 2020.[40]

### Reinfection rates and risk factors

International studies from Brazil, Italy, USA, Canada, United Kingdom and Poland have examined rates and risk factors for syphilis reinfection.[15, 42-46] Estimates of reinfection rates varied from 2.5% to 37% but with great variation in the composition and size of study populations, from all-population cohorts

to small cohorts exclusively of HIV-positive or MSM populations, timing, and testing methods (active screening or passive surveillance).[43, 47] Male sex, MSM, HIV coinfection, multiple sexual partners, and visiting sex-on-premises venues have all been associated with increased risk of syphilis reinfection.[42, 46]

A surveillance study published in 2013 followed infectious syphilis laboratory notifications in Sydney, NSW, between 2001 and 2011 and found that reinfections increased over time from 9% in 2001 to 19% in 2011. This result may be related to increased community testing. Reinfections were significantly more likely to be in HIV-positive individuals than HIV-negative individuals.[48]

Surveillance data reports from NSW Health have periodically examined reinfection rates. A report in 2020 found that the number of repeat notifications of infectious syphilis within 1 to 6 months from the time of initial diagnosis had increased since 2018. In 2020 there were 34 re-notifications of infectious syphilis, representing a 4.8-fold increase since 2016. All repeat notifications in the period 2016-2020 occurred in males.[39] The same report also found that the percentage of males with at least one repeat notification following an initial diagnosis of infectious syphilis has increased from 0.85% in 2016 to 1.8% in 2020.[39]

The timing of and factors related to reinfection for syphilis at a population-level have never been examined in detail in NSW. The results of this study will quantify the contribution of reinfection to the burden of disease for syphilis in NSW, provide information about the timing of reinfections, and help to identify factors which may predict reinfection, allowing for better targeting of public health interventions for syphilis prevention.

## Aims and objectives

The aim of this study was to quantify the burden of infectious syphilis reinfections in NSW between 2014 and 2021 and identify, describe and analyse differences in demographic and risk exposure characteristics between people who have a single syphilis notification and people who have repeat syphilis notifications. The study seeks to assess whether routinely collected enhanced surveillance data can predict who will be more likely to experience reinfection following their first syphilis event. This information can then be used to inform the timing and targeting of reinfection prevention interventions.

The study had three objectives:

- To quantify reported syphilis reinfections in NSW between 2014 and 2021 and describe their epidemiology;
- To determine the median time to reported reinfection in the cohort; and
- To examine factors that may be associated with reported syphilis reinfection.

## Methods

We conducted a retrospective cohort study using routinely collected state-wide public health surveillance data for infectious syphilis in NSW. The cohort was composed of all NSW residents aged 15 years and over with a first infectious syphilis notification with symptom onset between 01 January 2014 and 02 October 2021. Cohort data were analysed until 31 December 2021 for reinfections (the end of the study period).

The study's outcome of interest was infectious syphilis reinfection, defined as an individual with more than one confirmed or probable infectious syphilis infection event recorded in the NSW Notifiable Conditions Information Management System (NCIMS) within the study period. New syphilis events for individuals with a prior syphilis event are created in NCIMS according to the NSW case definition (Text box 1), which requires sufficient laboratory and clinical evidence to determine a new active infection and that the specimen was collected outside of the reinfection exclusion period (89 days).[20] The analysis included all notifications of infectious syphilis from the cohort in the study period in NSW, Australia, with age and sex data available. Where age or sex was missing for a notification, it was filled by imputation if the data were available from other events in the dataset for the same individual. If age or sex were missing and unable to be imputed from other notification events, those individuals were excluded.

Individuals with a known syphilis notification prior to 2014 were excluded as their risk of reinfection at the start of the study period was not equal. For the purposes of the survival analysis, people whose first infection occurred within 89 days of the end of the study period (between 03 October 2021 and 31 December 2021) were excluded from the analysis as they were still in the reinfection exclusion period and thus their total days at risk was less than zero.

### Text box 1: NSW Case definition – Infectious Syphilis [20]

**Confirmed case**

A confirmed case requires either:

- Laboratory definitive evidence **or**
- Laboratory suggestive evidence **and** clinical evidence.

**Laboratory definitive evidence**

Seroconversion in past two years: treponemal specific test[2] reactive when previous treponemal specific test non-reactive within past two years and the latest result is confirmed by either a reactive non-treponemal test[3] or a different reactive treponemal specific test **or**

A fourfold or greater rise in non-treponemal antibody titre compared with the most recently recorded titre within past two years, and a reactive treponemal specific test.

Laboratory suggestive evidence

Demonstration of *Treponema pallidum* by dark-field microscopy (not oral lesions), direct fluorescent antibody microscopy (direct antigen test), equivalent microscopic methods (e.g. silver stains), or DNA methods (e.g. nucleic acid testing) or

A reactive treponemal specific test confirmed by either a reactive non-treponemal test or a different reactive treponemal specific test or

A reactive non-treponemal test confirmed by a treponemal specific test.

Clinical evidence

Presence of a primary chancre (or ulcer) or

Clinical signs of secondary syphilis.

Probable case

A probable case requires that case does not meet the criteria for a confirmed case and either:

a) In a person with no known previous reactive serology: no history of adequate treatment of syphilis, or endemic treponemal disease, and

- Contact with an infectious case and laboratory suggestive evidence or
- Laboratory suggestive evidence and RPR ≥16 or
- Positive syphilis IgM and laboratory suggestive evidence or

b) In a person with previous reactive serology: a fourfold or greater rise in non- treponemal antibody titre when the previous serology was done more than two years ago and

- Contact with an infectious case or
- Positive syphilis IgM.

[2] Treponemal specific tests are: IgG or total Ab immunoassay (EIA or CLIA), Treponema pallidum haemagglutination assay (TPHA), Treponema pallidum particle agglutination assay (TPPA), Fluorescent Treponemal Antibody Absorption (FTA-Abs), 19S-IgM antibody test, or IgM immunoassay, Treponemal Ab specific immunochromatography (ICT) assay.

[3] Non-treponemal tests are: Rapid Plasma Reagin (RPR), Venereal Disease Research Laboratory (VDRL). See section 8 for further details.

*Determining when a new notification is a new event*

A positive VDRL/RPR serology result will be treated as a new event of confirmed or probable Infectious syphilis where there is evidence of a previously adequately treated infectious syphilis infection AND the specimen was taken outside the re-infection period (89 days).

Laboratory definitive evidence for reinfection in an individual with a previously adequately treated infectious syphilis infection: A fourfold or greater rise in non-treponemal antibody titre on RPR or VDRL compared with the most recently recorded titre within past two years OR a new positive PCR result from a specimen taken from a chancre.

Under NSW control guidelines blood should be collected for baseline RPR at the time of the first treatment dose to assess response to treatment and check for re-infection. RPR testing at 3-6 months and 12 months following treatment is recommended to determine the response of treatment.

## Literature review

We conducted a search of published literature containing syphilis incidence rates reported as cases per 100 person-years, from cohort studies containing 300 or more subjects. The literature review strategy is included at Appendix A. The review returned 35 articles.

## Statistical methods

We calculated the proportion of the cohort with more than one notification in the study period, the range and frequency of notifications per person in the study period, and the proportion of notifications in the study period that were repeat notifications. We described the cohort by demographic, clinical and exposure risk factor information, and reinfection status. We described the proportion of individuals with repeat notifications in each local health district (LHD) geographically using a choropleth map.

For the survival analysis we calculated total days at risk for each individual, using their total time in the study (from date of their first infection to the end of the study period) and removing the reinfection exclusion window of 89 days following each infection. The outcome of interest (failure) was first reinfection. Individuals without a recorded reinfection were censored on the last day of the study period (31 December 2021).

We calculated a reinfection incidence rate using negative binomial regression due to over-dispersal of the reinfection count data. This rate is calculated using the number of reinfections per days at-risk for all individuals in the cohort, not just those who experienced the failure (reinfection). The choice of negative binomial distribution was confirmed by summarising the reinfection count and finding that the mean (0.14997) is less than the variance (0.44126). We generated univariate Kaplan-Meier failure curves for variables of interest, excluding missing values, and calculated the median time to first reinfection for those who became reinfected.

We used a Cox regression analysis to investigate the effect of exposure variables (age, sex, previous STI notification, PrEP use, sex work, MSM sexual exposure, Indigenous status, country of birth, remoteness) on likelihood of reinfection. To improve the strength of the regression analysis we collapsed the five-year age groups into ten-year age groups.

To account for the volume of missing data and analyse its impact, we undertook a sensitivity analysis by developing and comparing three Cox regression models (Table 1). We used a correlation matrix of coefficients to identify collinearity in each model, and likelihood-ratio tests to confirm the improved performance of the reduced models. We also used likelihood-ratio tests to examine interactions

between variables in each of the models. We used Cox-Snell residuals to check the reliability of each model by comparing the difference between the observed data points and predicted values.

Table 1: Summary of the three models developed for the sensitivity analysis

| Characteristics | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Sample | Full cohort | Only participants with complete data for all variables | Only participants with first syphilis event on or after 01 Jan 2017 |
| Management of missing data | Missing data considered as own category | No missing data | Missing data considered as own category |
| Time period | 01 January 2014 to 31 December 2021 | 01 January 2014 to 31 December 2021 | 01 January 2017 to 31 December 2021 |
| Rationale | Reference model, unaltered dataset | To remove impact of missing data | To mitigate impact of missing PrEP use data (PrEP variable largely incomplete 2014-2016) |

Analyses were conducted in STATA /IC v16, with a p value <0.05 considered as the level of statistical significance. The maps were produced using R (version 4.1.0).

## Data source

Demographic, epidemiological and laboratory data were extracted from the NSW Notifiable Conditions Information Management System (NCIMS). NCIMS contains records of all people notified to NSW Health with a notifiable condition under the NSW Public Health Act. Due to privacy restrictions in the NCIMS dataset, HIV status is unknown for all members of the cohort.

Syphilis is notifiable in NSW under Schedule 2 of the *Public Health Act 2010, No 127*, by medical practitioners, hospital chief executives, and laboratories. In practice, almost all notifications in NSW are generated by laboratories from positive diagnostic tests.

Cases of syphilis in NSW are classified as either infectious syphilis (less than two years duration: includes primary, secondary and early latent) or syphilis (more than 2 years or unknown duration).

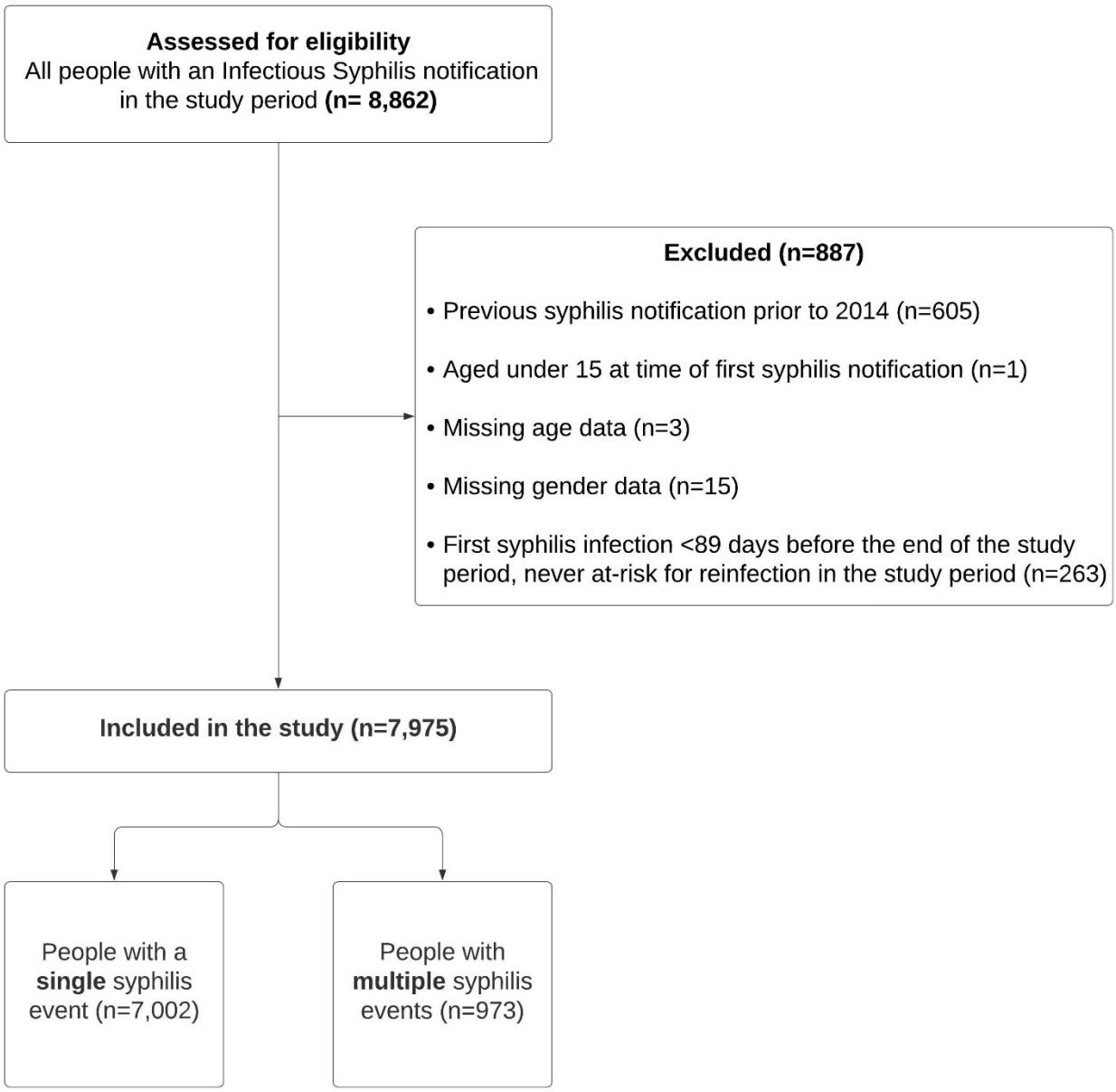
Syphilis laboratory diagnosis reports are interpreted for each individual in the context of any prior results, with a new event created in NCIMS when the criteria are met for infectious syphilis or syphilis (more than 2 years duration) according to the case definition. All individuals have a unique person identifier in NCIMS and each new event is assigned unique event ID.

## Results

### Cohort characteristics

The cohort comprised 7,975 individuals with a first recorded infectious syphilis notification in NSW with symptom onset between 01 January 2014 and 02 October 2021. Individuals with a first notification between 03 October and 31 December 2021 were excluded as they were never at risk of reinfection during the study period due to the 89-day reinfection exclusion period under the NSW infectious syphilis case definition (Figure 3).

**Figure 3: Flow diagram of participants in the study, NSW, Australia,** 2014–2021



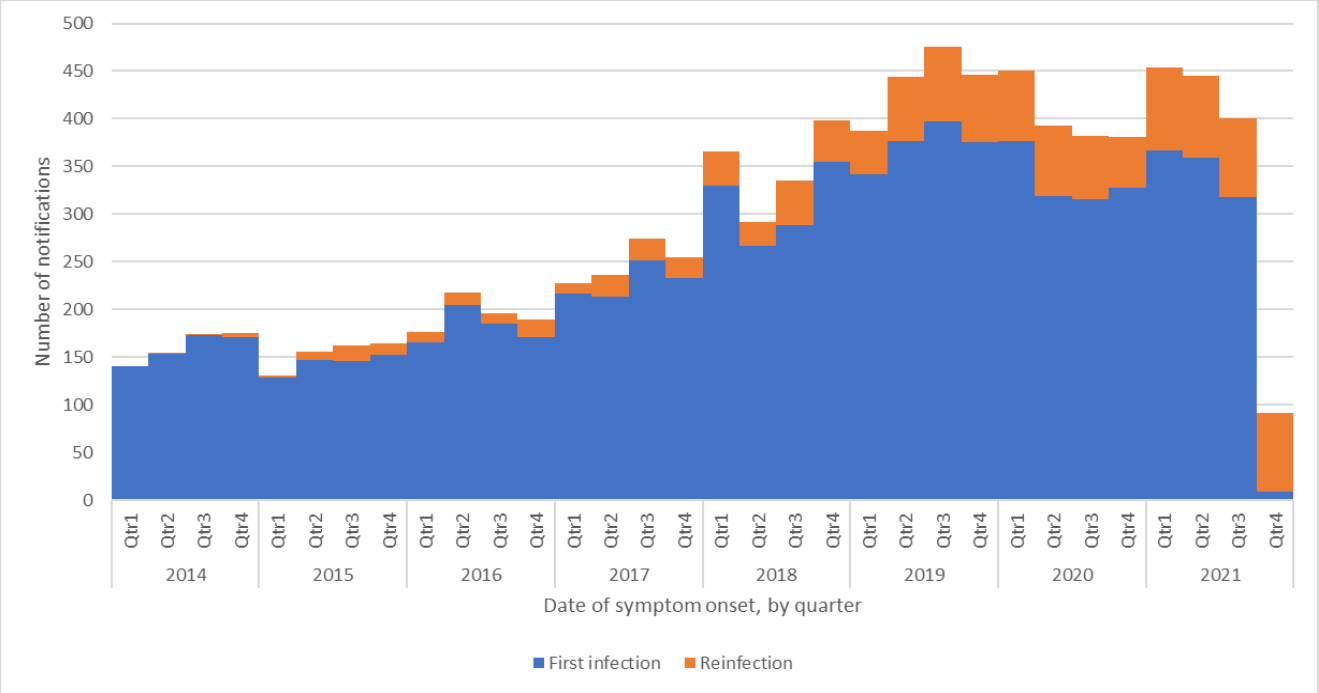
During the study period, from 01 January 2014 to 31 December 2021, reinfections were identified in 973 people (12.2% of the cohort, range of notifications per person between 1 and 7) (Table 2). There were 9,171 confirmed or probable infectious syphilis notifications among the cohort; 1,196 (13%) were reinfections in previously infected and treated individuals.

**Table 2: Distribution of multiple Infectious Syphilis notifications among the cohort**

| Number of infections notified | Frequency | Total observations |
|---|---|---|
| 1 | 7,002 | 7,002 |
| 2 | 784 | 1,568 |
| 3 | 163 | 489 |
| 4 | 20 | 80 |
| 5 | 5 | 25 |
| 6 | 0 | 0 |
| 7 | 1 | 7 |
| Total | 7,975 | 9,171 |

Annual notifications of infectious syphilis increased 116% over the study period, from 644 in 2014 to 1,392 in 2021 (Figure 4). The proportion of individuals in the cohort with repeat syphilis notifications also increased over this period, from 0.9% of notifications in 2014 to 20.5% of notifications in 2021. This trend is expected as individuals in the cohort have a greater opportunity to become reinfected as their time in the study increases.

**Figure 4: Epi curve of all notifications from the study cohort, by first infection and reinfection, 01 January 2014–31 December 2021**



The cohort was 92.8% male, median age at first syphilis event was 34 (IQR 28-44), and 91.3% resided in major metropolitan areas (Table 3). Of the males with sexual history information available, 85.5% (5,131/5,999) reported same-sex sexual activity.

In the 12 months to one month prior to their first infectious syphilis notification in NSW, 22.7% of the cohort had a notification for chlamydia and/or gonorrhoea in NSW.

Data on current sex worker status, use of HIV PrEP, and place of birth are missing for a sizeable proportion of the cohort. While 2.6% of the cohort reported being a current sex worker at the time of their first infection, data for this variable are missing for a quarter (24.9%) of the cohort.

Use of HIV PrEP data is missing for more than half of the cohort (52.9%) at time of first notification. This has been affected by the relative lack of availability of HIV PrEP in the first three years of the study period and is discussed further during the multivariate Cox regression analysis.

Data on place of birth is missing for 30.3% of the cohort. For those with data recorded for this variable, 54.8% (3,030/5,562) were born in Australia.

**Table 3: Cohort characteristics by reinfection status, at enrolment (time of first infectious syphilis diagnosis), NSW, Australia, 01 January 2014–02 October 2021 (n=7,975)**

| | People with a SINGLE syphilis event n=7,002 | People with REPEAT syphilis events n=973 | Whole cohort n=7,975 | p-value^ |
|---|---|---|---|---|
| **Sex (%)** | | | | <0.001 |
| Female | 524 (7.5) | 19 (2.0) | 543 (6.8) | |
| Male | 6,449 (92.1) | 952 (97.8) | 7,401 (92.8) | |
| Transgender | 29 (0.4) | 2 (0.2) | 31 (0.4) | |
| **Age group (%)** | | | | <0.001 |
| 15-19 yrs | 139 (2.0) | 7 (0.7) | 146 (1.8) | |
| 20-24 yrs | 798 (11.4) | 78 (8.0) | 876 (11.0) | |
| 25-29 yrs | 1,352 (19.3) | 163 (16.8) | 1,515 (19.0) | |
| 30-34 yrs | 1,262 (18.0) | 200 (20.6) | 1,462 (18.3) | |
| 35-39 yrs | 1,022 (14.6) | 150 (15.4) | 1,172 (14.7) | |
| 40-44 yrs | 728 (10.4) | 121 (12.4) | 849 (10.6) | |
| 45-49 yrs | 594 (8.5) | 122 (12.5) | 716 (9.0) | |
| 50-54 yrs | 487 (7.0) | 68 (7.0) | 555 (7.0) | |
| 55-59 yrs | 300 (4.3) | 42 (4.3) | 342 (4.3) | |
| 60+ yrs | 320 (4.6) | 22 (2.3) | 342 (4.3) | |

| | | | | |
|---|---|---|---|---|
| **Remoteness (%) *** | | | | <0.001 |
| Major Cities | 6,345 (90.6) | 939 (96.5) | 7,284 (91.3) | |
| Regional | 559 (8.0) | 31 (3.2) | 590 (7.4) | |
| Remote & Very remote | 15 (0.2) | 0 (0.0) | 15 (0.2) | |
| Unknown or missing | 81 (1.2) | 3 (0.3) | 84 (1.1) | |
| **Aboriginal and/or Torres Strait Islander (%)** | | | | <0.001 |
| Yes | 306 (4.4) | 34 (3.5) | 340 (4.3) | |
| No | 5,863 (83.7) | 872 (89.6) | 6,735 (84.5) | |
| Unknown or missing | 833 (11.9) | 67 (6.9) | 900 (11.3) | |
| **Country of birth (%)** | | | | <0.001 |
| Australia | 2,589 (37.0) | 441 (45.3) | 3,030 (38.0) | |
| Overseas | 2,182 (31.2) | 350 (36.0) | 2,532 (31.7) | |
| Unknown or missing | 2,231 (31.9) | 182 (18.7) | 2,413 (30.3) | |
| **Men who have sex with men (MSM) (%) **** | | | | <0.001 |
| Yes | 4,423 (63.2) | 708 (72.8) | 5,131 (64.3) | |
| No | 1,343 (19.1) | 68 (7.0) | 1,411 (17.7) | |
| Unknown or missing | 1,236 (17.7) | 197 (20.2) | 1,433 (18.0) | |
| **Prior STI (365-30 days prior to first syphilis event) (%) ***** | | | | <0.001 |
| Yes | 1,456 (20.8) | 352 (36.2) | 1,808 (22.7) | |
| No | 5,546 (79.2) | 621 (63.8) | 6,167 (77.3) | |
| **Current sex worker (%)** | | | | 0.14 |
| Yes | 187 (2.7) | 19 (2.0) | 206 (2.6) | |
| No | 5,095 (72.8) | 692 (71.1) | 5,787 (72.6) | |
| Unknown or missing | 1,720 (24.6) | 262 (26.9) | 1,982 (24.9) | |
| **PrEP user (%)** | | | | <0.001 |
| Yes | 785 (11.2) | 110 (11.3) | 895 (11.2) | |
| No | 2,624 (37.5) | 241 (24.8) | 2,865 (35.9) | |
| Unknown or missing | 3,593 (51.3) | 622 (63.9) | 4,215 (52.9) | |

PrEP user: Pre-Exposure Prophylaxis for HIV

* Remoteness: The Australian Bureau of Statistics Australian Statistical Geography Standard (ASGS) Remoteness Structure is used to derive this variable automatically in NCIMS from the address of an individual. Remoteness Areas divide Australia into 5 classes of remoteness using a measure of relative access to services.[49]

** MSM: Where sex was recorded as male and sexual history recorded either "Person(s) of the same sex only" or "Persons of both sexes."

*** Prior STI: A gonorrhoea or chlamydia notification between 12 months and one month prior to first syphilis notification. This variable was designed to act as an indicator of sexual exposure risk behaviour.[50, 51]

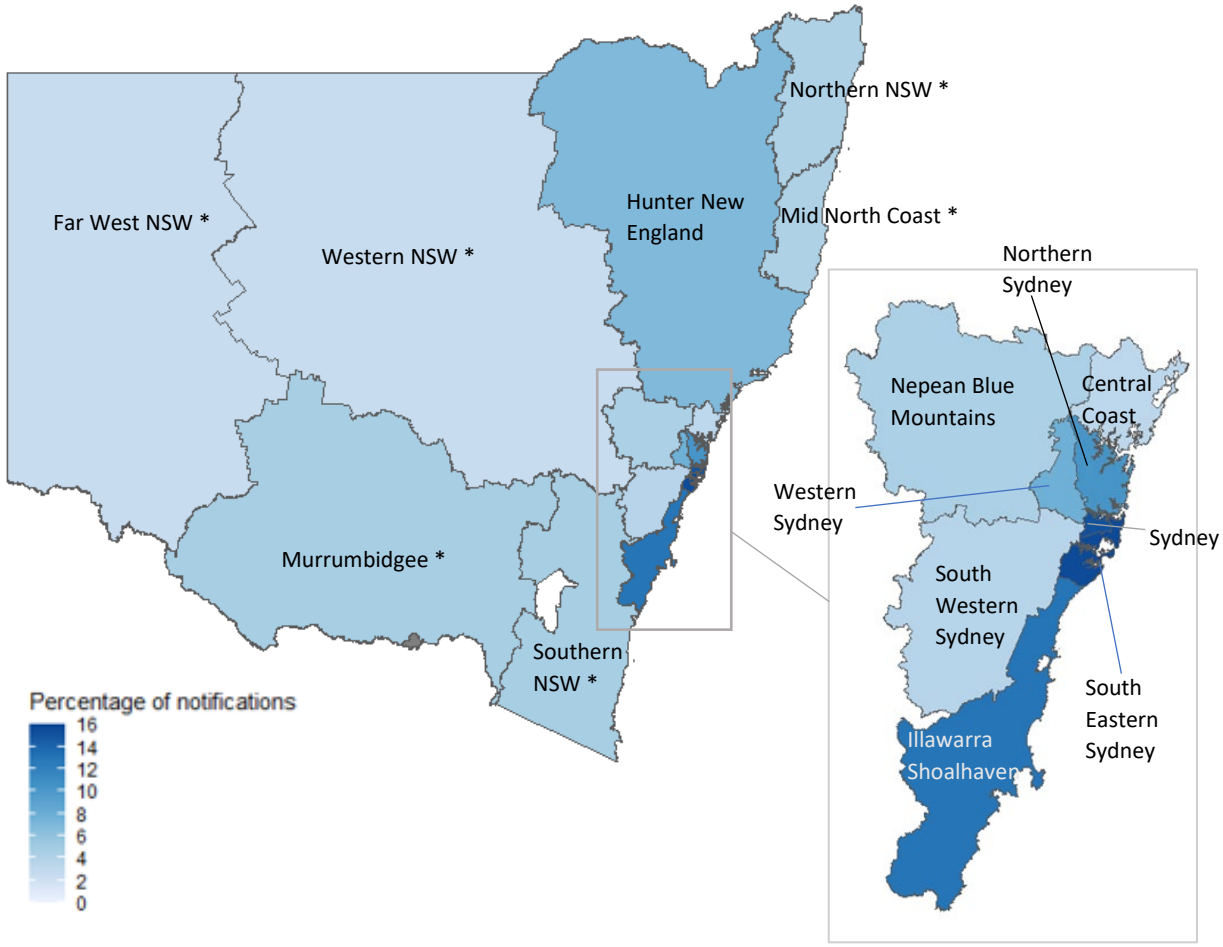
^ Chi-squared test comparison between single syphilis individuals and repeat syphilis individuals. P values < 0.05 were considered statistically significant.

On comparison, the differences in participant characteristics between the two groups are statistically significant for all variables except current sex worker status.

The metropolitan local health districts (LHDs) of South Eastern Sydney (covering inner city Sydney and the eastern and south eastern suburbs) and Sydney (covering the inner west suburbs south of the Parramatta river) together were home to 61.7% of the cohort at the time of their first notification. Of

the 973 people with repeat syphilis notifications, 760 (78.1%) were residents of South Eastern Sydney or Sydney LHDs.

**Figure 5: Percentage of notifications that are repeat notifications, by Local Health District of residence, NSW, Australia, 01 January 2014–31 December 2021. Greater Metropolitan Sydney LHDs in insert.**




*Regional LHDs have been combined due to small numbers: Far West and Western NSW, Mid North Coast and Northern NSW, Murrumbidgee and Southern NSW.

## Reinfection incidence rate

The overall incidence rate of reported reinfection across the cohort was 4.93 (95% CI 4.61-5.27) per 100 person years.

## Literature review: Incidence rates

Published cohort studies that have calculated a syphilis incidence rate have been conducted in high-risk populations, such as HIV positive people, sex workers, or exclusively MSM populations, often with small cohorts, and from a time period before widespread highly active antiretroviral therapy (HAART) and PrEP use. Study designs vary greatly, with some describing active follow-up of participants while

others have a more passive collection of test results similar to routine surveillance. This will have an impact on case detection and incidence rates.

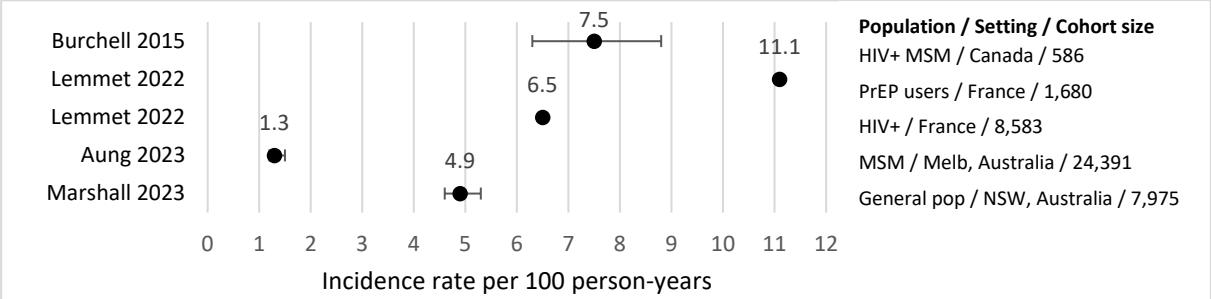
Published incidence rates from around the world range from 0.4 cases per 100 person-years[52] to 18.7 cases per 100 person-years.[53] The lowest incidence rates from the literature review are in exclusively female cohorts, with 0.4 and 1.1 cases per 100 person-years reported in studies of female sex workers in Australia[52] and China[54] respectively and 0.6 cases per 100 person-years reported in a cohort of women using injectable contraception enrolled in a HIV PrEP clinical trial in South Africa.[55]

Incidence rates that are comparable to the reinfection incidence rate in this study have been observed in exclusively MSM and/or HIV+ populations in Thailand[56], Japan[57], USA[58], Australia[59], and China.[60] Of particular interest in the USA study, which employed a similar retrospective cohort study design without active follow-up of participants.[58] The study reviewed medical records from four clinics where HIV+ people receive care and had a similar cohort size (8,455 people living with HIV) and a five year study period from 2014 to 2018. It found a rate of incident syphilis of 4.7 (95% CI 4.5–5.0) cases per 100 person-years, with diagnosis rates highest among younger cisgender MSM and transgender women, people who inject drugs, and those with detectable HIV RNA.[58]

A smaller study of 617 MSM in Sydney, NSW, from 2009 to 2018 found an incidence rate of 5.5 (95% CI 4.4–6.8) per 100 person-years.[59] The characteristics of the cohort in this smaller study are similar to those of the current reinfection study cohort, which, despite being a general population cohort drawn from routine surveillance, is overwhelmingly male, MSM, and metro residents. The reinfection incidence rate of 4.93 per 100 person-years calculated from a much larger cohort complements and corroborates the incidence rate of the smaller study.

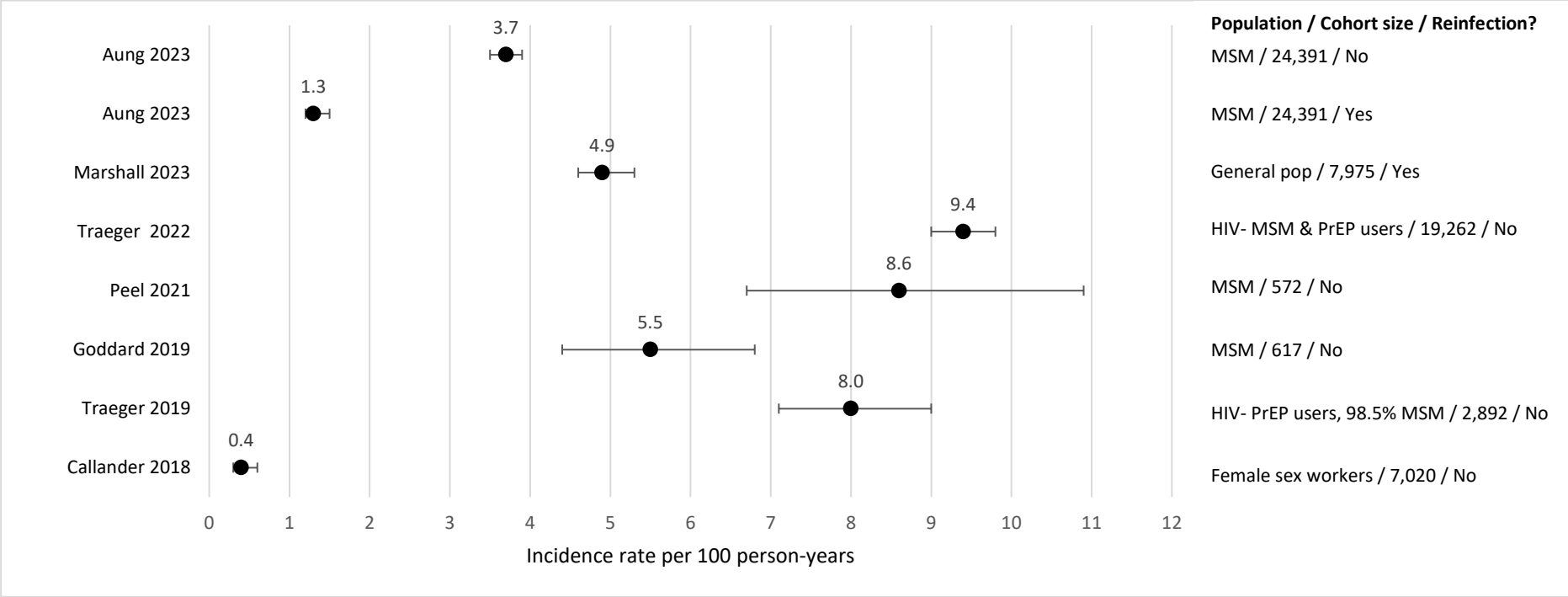
In the few studies that report reinfection incidence rates, these range from 1.3 per 100 person-years[61] to 11.1 per 100 person-years (Figure 6).[62] A large 2023 Australian study of MSM reported an initial syphilis incidence rate of 3.7 (95% CI 3.5–3.9) per 100 person-years and a reinfection incidence rate of 1.3 (95% CI 1.2–1.5) per 100 person-years.[61]

Figure 6: Forest plot of published reinfection incidence rates per 100 person-years, with 95% CIs where available, and information on study population, setting and cohort size. This study reinfection incidence rate included for context (Marshall 2023).[44, 61, 62]




Looking exclusively at studies published on Australian cohorts, this study with its general population cohort sits in the middle of the reported rates (Figure 7).

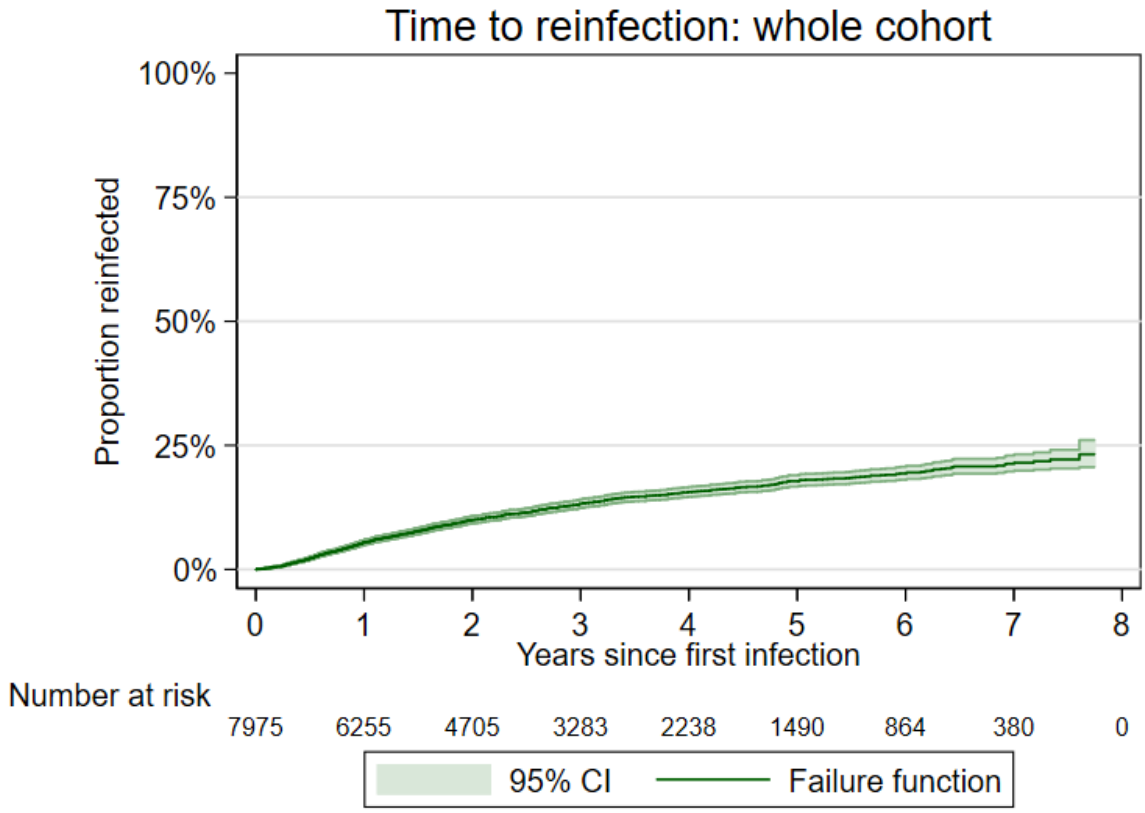
Figure 7: Forest plot of published Australian cohort incidence rates per 100 person-years, with 95% CIs, and information on study population, cohort size, and whether the rate is for reinfection. This study reinfection incidence rate included for context (Marshall 2023).[52, 59, 61, 63-65]



## Time to first reinfection

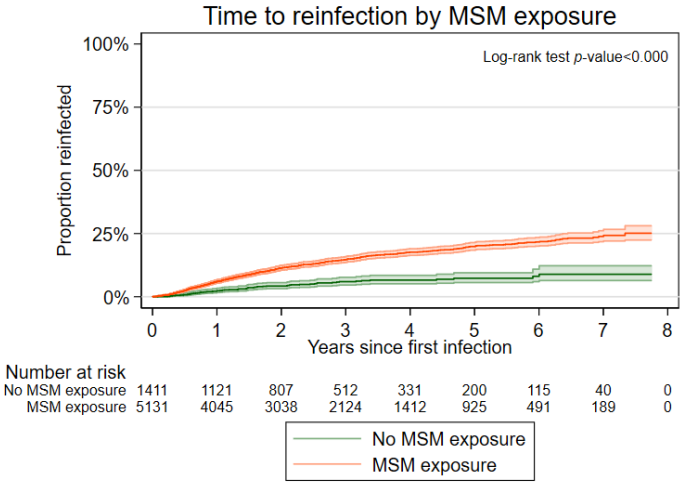
A median time to reinfection could not be calculated as proportions reinfected did not reach 50% during the study period of eight years (Figure 8). Differences between univariate Kaplan Meier failure curves did demonstrate faster time to first reinfection by individual variables of prior STI, male sex, metro residence, and MSM activity (Figure 9).

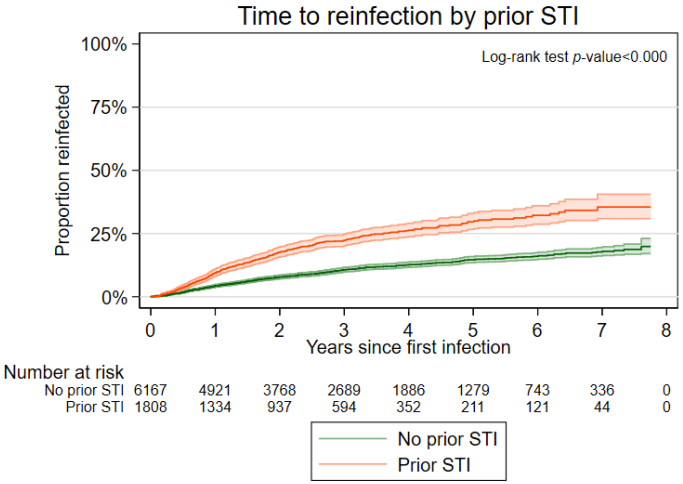
**Figure 8: Kaplan-Meier failure graph for time to reinfection for the whole cohort (n=7,975), NSW, Australia, 01 January 2014–31 December 2021. ***

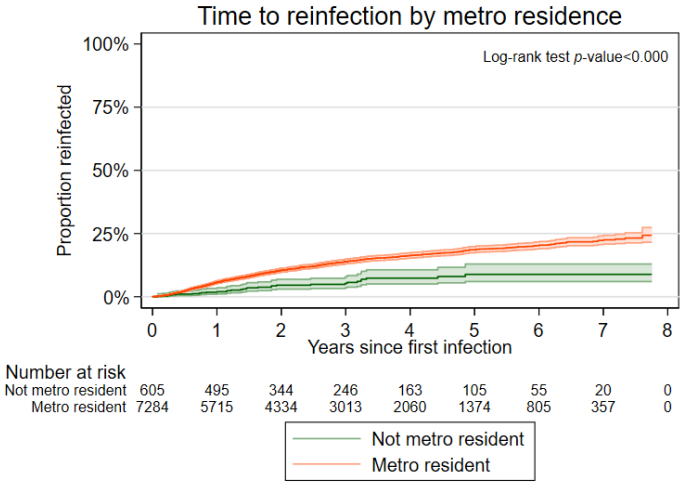


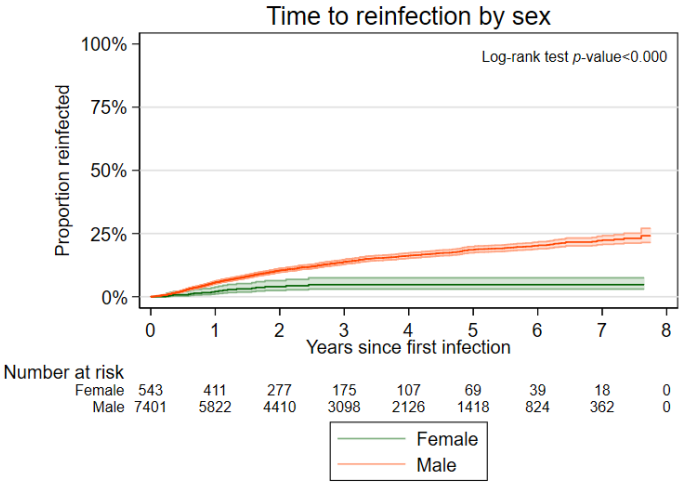

*The 'number at risk' decreases as individuals either become reinfected or are censored.

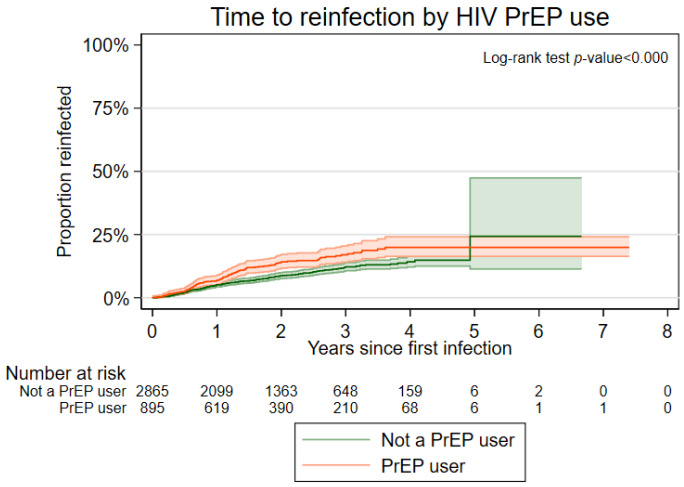
Figure 9: Kaplan-Meier graphs of time to Infectious Syphilis reinfection by demographic, clinical and risk exposure characteristics, NSW, Australia, 01 January 2014–31 December 2021 (n=7,975). Shaded areas represent the respective 95% confidence intervals.

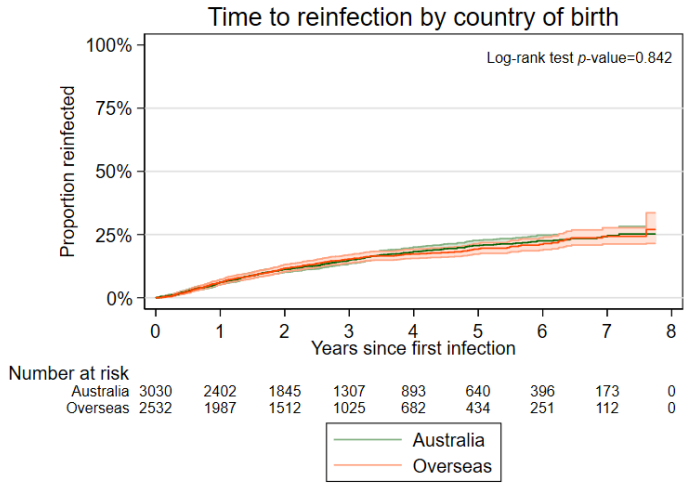


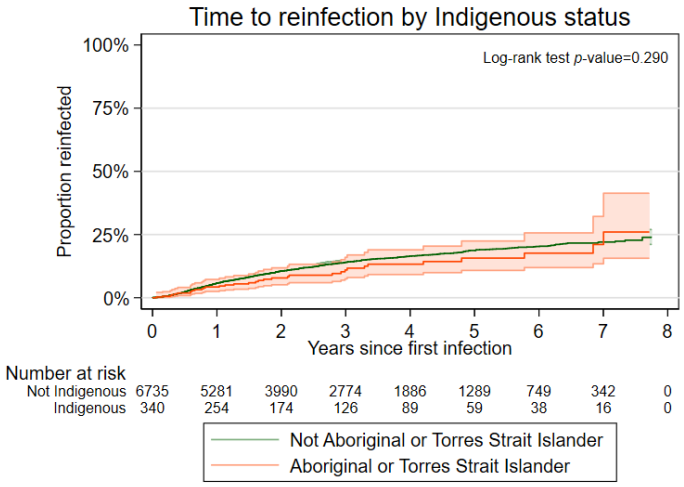



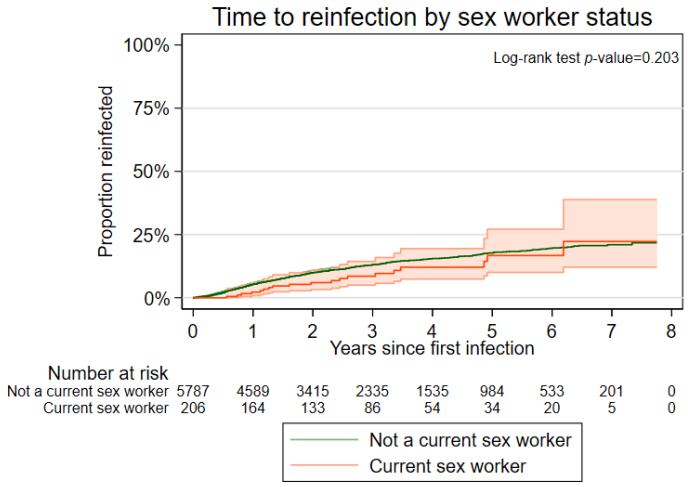




Time to reinfection by HIV PrEP use
Log-rank test p-value<0.000
Proportion reinfected
100%
75%
50%
25%
0%
0 1 2 3 4 5 6 7 8
Years since first infection
Number at risk
Not a PrEP user 2865 2099 1363 648 159 6 2 0 0
PrEP user 895 619 390 210 68 6 1 1 0
Not a PrEP user
PrEP user

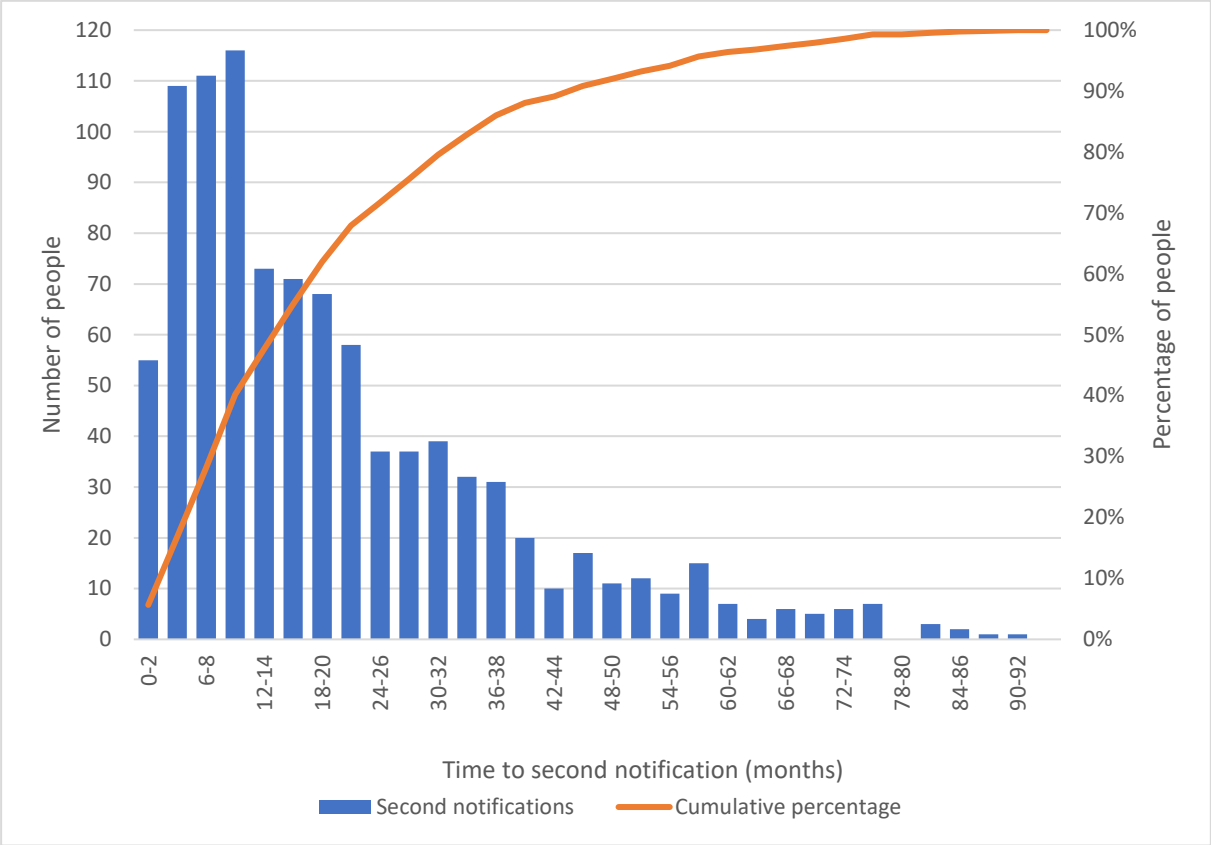

Time to reinfection by country of birth
Log-rank test p-value=0.842
Proportion reinfected
100%
75%
50%
25%
0%
0 1 2 3 4 5 6 7 8
Years since first infection
Number at risk
Australia 3030 2402 1845 1307 893 640 396 173 0
Overseas 2532 1987 1512 1025 682 434 251 112 0
Australia
Overseas


Time to reinfection by Indigenous status
Log-rank test p-value=0.290
Proportion reinfected
100%
75%
50%
25%
0%
0 1 2 3 4 5 6 7 8
Years since first infection
Number at risk
Not Indigenous 6735 5281 3990 2774 1886 1289 749 342 0
Indigenous 340 254 174 126 89 59 38 16 0
Not Aboriginal or Torres Strait Islander
Aboriginal or Torres Strait Islander


Time to reinfection by sex worker status
Log-rank test p-value=0.203
Proportion reinfected
100%
75%
50%
25%
0%
0 1 2 3 4 5 6 7 8
Years since first infection
Number at risk
Not a current sex worker 5787 4589 3415 2335 1535 984 533 201 0
Current sex worker 206 164 133 86 54 34 20 5 0
Not a current sex worker
Current sex worker

The median time to first reinfection for those who recorded a reinfection in the study period was 485 days (IQR 240–901 days) (Figure 10). The shortest time to reinfection was two days (after the end of the 89-day reinfection exclusion period); the longest time to reinfection was 2,778 days.

**Figure 10: Time to second notification for those who record a repeat notification during the study period, 01 January 2014–31 December 2021, (n=973)**



## Cox regression: Sensitivity analysis

The three model sample sizes and reinfection characteristics are summarised in Table 4. The first model included the full sample of all cases and analysed missing data as its own category (n=7,975). The second model was fit to a smaller sample of complete cases only in the dataset, and excluded any case with a missing value for sex, MSM, PrEP, current sex worker, born in Australia, metro residence, prior STI, or indigenous status (n=2,277). The third model included only cases from 01 January 2017 to 31 December 2021, to investigate the impact of PrEP use on the reinfection outcome in the dataset (n=6,037). This sample was chosen due to the volume of missing data for PrEP in the dataset, and its potential to skew the results. PrEP use data was missing from 99.8% of notifications in 2014, 99.7% in 2015, and 96.7% in 2016. This dropped to 57.6% in 2017 and 35.8% in 2018 (Table 5).

**Table 4: Description of the samples used in the three Cox regression models, NSW, Australia, 01 January 2014–31 December 2021 (Total cohort n=7,975)**

| Model and sample | Number of cases included | Number with a single syphilis event | Number with multiple syphilis events | % Repeaters |
|---|---|---|---|---|
| **Model 1**<br>Full sample, missing coded as own category | 7,975 | 7,002 | 973 | 12.2 |
| **Model 2**<br>Complete case only analysis<br>(all variables, no missing values) | 2,277 | 2,044 | 233 | 10.2 |
| **Model 3**<br>2017–2021 cases only, accounting for volume of missing PrEP values 2014–2016 | 6,037 | 5,420 | 617 | 10.2 |

**Table 5: Data for 'Current PrEP user' in the dataset, breakdown by year and response category, all notifications, 01 January 2014–31 December 2021.**

| PrEP user<br>n (%) | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | Total |
|---|---|---|---|---|---|---|---|---|---|
| Yes | 1<br>(0.2) | 0<br>(0.0) | 9<br>(1.2) | 125<br>(12.6) | 209<br>(15.0) | 251<br>(14.3) | 258<br>(16.1) | 235<br>(16.9) | 1088<br>(11.9) |
| No | 0<br>(0.0) | 2<br>(0.3) | 17<br>(2.2) | 296<br>(29.8) | 684<br>(49.2) | 858<br>(48.9) | 808<br>(50.3) | 624<br>(44.8) | 3289<br>(35.9) |
| Missing | 643<br>(99.8) | 611<br>(99.7) | 753<br>(96.7) | 572<br>(57.6) | 498<br>(35.8) | 644<br>(36.7) | 540<br>(33.6) | 533<br>(38.3) | 4794<br>(52.3) |
| Total | 644 | 613 | 779 | 993 | 1391 | 1753 | 1606 | 1392 | 9,171 |

I removed the sex variable from all three models due to collinearity with the MSM variable and identified effect modification between strata of the MSM and Prior STI variables. The Cox-Snell residuals demonstrated good fit for all three models.

All three models produced similar results, with older age group at first syphilis event (35–44 or 45–54 years), being MSM, and having a prior STI all exhibiting statistically significant increased adjusted hazard ratios (aHR) for reinfection across the three models (Table 6). The magnitude of effect for these three significant indicators remained steady across the models, with differences in the width of the 95% confidence intervals corresponding to the sample size of the model.

Table 6: Concordance between significant variables across three models

| aHR (95% CI) | Variable | | | | |
|---|---|---|---|---|---|
| | Age group 35-44 yrs (compared to age group 15-24) | Age group 45-54 yrs (compared to age group 15-24) | MSM (compared to not MSM) | Prior STI (compared to no prior STI) | MSM#Prior STI (Person is MSM **and** has a prior STI) |
| **Model 1 (n=7,975)** | 1.60 (1.16–1.86) | 1.73 (1.34–2.23) | 2.76 (2.04–3.74) | 5.03 (3.00–8.44) | 0.36 (0.21–0.61) |
| **Model 2 (n=2,277)** | 1.76 (1.05–2.95) | 1.93 (1.11–3.35) | 2.12 (1.21–3.72) | 5.84 (2.44–14.01) | 0.34 (0.14–0.85) |
| **Model 3 (n=6,037)** | 1.56 (1.14 –2.14) | 1.69 (1.21–2.36) | 2.49 (1.73–3.58) | 5.10 (2.87–9.07) | 0.36 (0.20–0.66) |

Effect modification between strata of MSM and Prior STI was also statistically significant across all three models, and produced a reduction in overall risk of reinfection when an individual was MSM and had a prior STI event (Model 1 aHR 0.36, 95% CI 0.21–0.61, $p<0.001$). This reduction of risk must be interpreted in the context of the significantly elevated risks of both MSM status and a prior STI, not as a standalone measure.

Older age group (25–34 years) and metro residence were both significant with slight increased risk in Model 1 and Model 3, but not in Model 2. The smaller sample size of Model 2 likely decreased the power to detect the effect. PrEP use, current sex worker status, Indigenous status, and country of birth were not significant in any model.

### Model selection

All three models demonstrated the same results for significance of the variables, although the magnitude of significance varied between the three models. The purpose of Model 3 was to investigate the impact of PrEP in the cohort by removing the bulk of the observations for which this

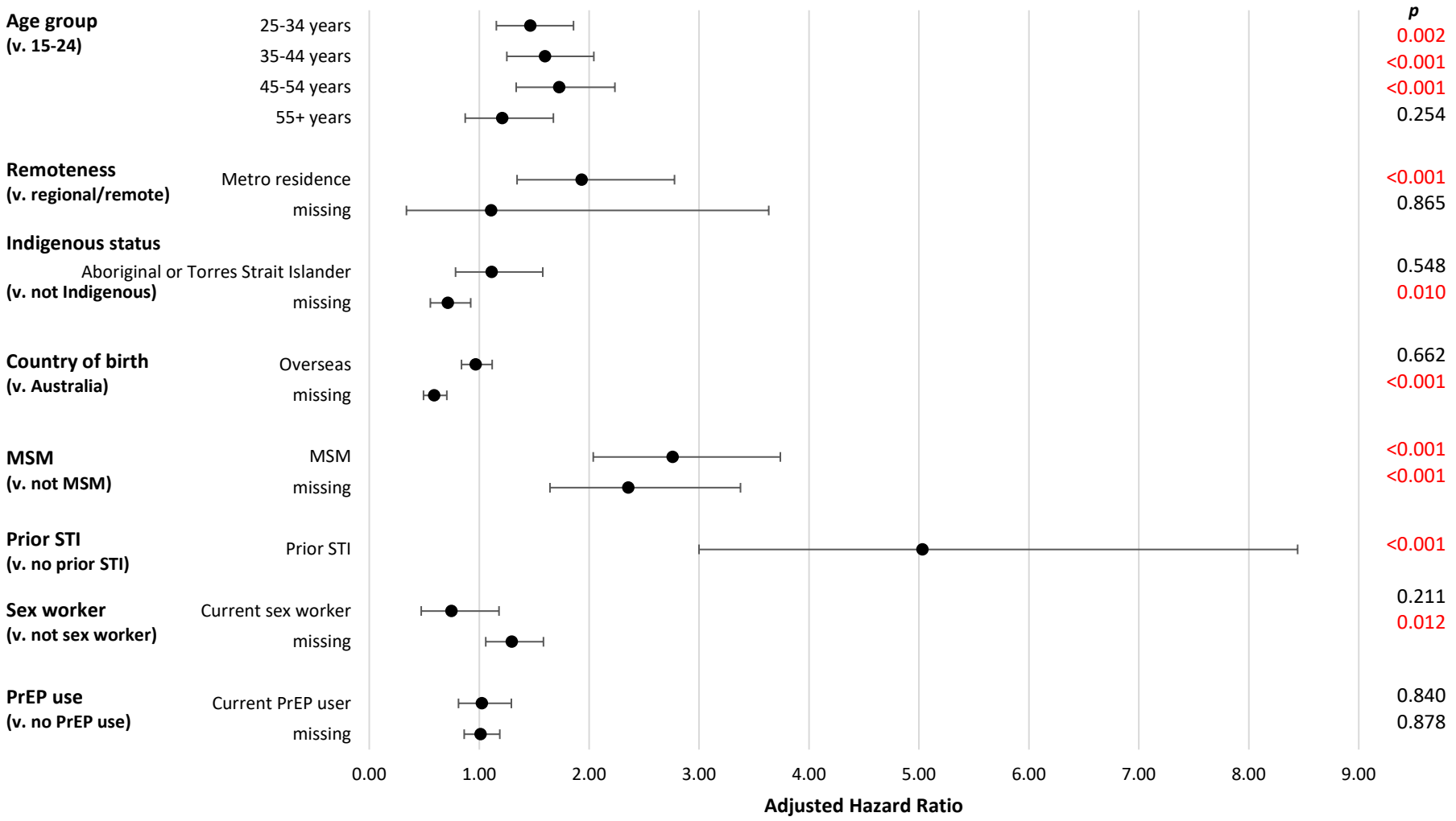
variable was missing. Despite this, PrEP did not demonstrate any effect. As this model did not achieve this aim, and generated very similar results to Model 1, I chose to discard it.

A comparison of Model 1 and Model 2 allowed me to examine the effect of missing values on the model. The removal of missing values from Model 2 did not lead to major changes in the results. Older age group 25-34 and metro residence lost their significance, but the confidence intervals of all variables increased due to the reduction in sample size. I selected Model 1 as the final model due to its larger sample size and greater power.

### Cox regression: Factors associated with reinfection

Four factors produce statistically significant increased hazard ratios in the model: being a man who has sex with men (MSM) (aHR 2.76, 95%CI 2.04–3.74, p<0.001), having a prior STI (chlamydia or gonorrhoea) notification in the 12 months to one month prior to a first infectious syphilis notification (aHR 5.03, 95%CI 3.00–8.44, p<0.001), being a resident of metro area (aHR 1.93, 95%CI 1.34–2.78, p<0.001), and being in an older age group at first infectious syphilis notification, compared to the reference age group of 15–24 years, such as 25–34 years (aHR 1.47, 95%CI 1.16–1.86, p=0.002), 35–44 years (aHR 1.60, 95%CI 1.25–2.04, p<0.001), or 45–55 years (aHR 1.73, 95%CI 1.34–2.23, p<0.001) (Figure 11).

Figure 11: Forest plot of adjusted hazard ratios with 95% CI for infectious syphilis reinfection by demographic, clinical and risk exposure main effects, full cohort (n=7,975), 01 January 2014–31 December 2021.



## Discussion

To our knowledge, this is the first study to examine syphilis reinfection at population-level in NSW. The study found that 12.2% of the cohort experienced a syphilis reinfection over the study period, and that 13% of infectious syphilis notifications in NSW between 2014 and 2021 are repeat infections in previously infected and treated individuals. The reinfection incidence rate for the whole-of-population cohort was 4.93 (95% CI 4.61–5.27) per 100 person-years. Evidence related to syphilis reinfection incidence in general population cohorts is scarce. A literature review contextualised the rate produced in this study and demonstrated that published incidence rates from studies with similar designs and cohort sizes are comparable to this study, which supports the validity of this result.

The median time to reinfection for the whole cohort was greater than eight years. The median time to reinfection for those individuals in the cohort who became reinfected was 485 days (IQR 240–901 days). Factors associated with reinfection include MSM exposure (aHR 2.76, CI 2.04–3.74, p<0.001) and a STI notification in the prior 12 months (aHR 5.03, CI 3.00–8.44, p<0.001). Use of HIV PrEP was not associated with reinfection.

Evidence of prior STI as a strong predictor of syphilis reinfection is an important finding both to improve targeting of syphilis reinfection prevention activities and to strengthen screening guidelines. Current Commonwealth pregnancy care guidelines recommend repeat testing "early in the third trimester (28–32 weeks) and at the time of birth for women at high risk of infection or reinfection," to prevent congenital syphilis.[66] The guidelines define a pregnant woman at high risk of syphilis infection or reinfection as someone living in a declared outbreak area or an area of known high prevalence, or having a sexual partner who resides in such an area, having previously had infectious syphilis during a pregnancy, engaging in intravenous substance use during pregnancy, or having a STI during the current pregnancy or within the previous 12 months.[66] The guidelines recognise other factors related to sexual partners that increase a pregnant woman's risk of syphilis infection or reinfection, including being a sexual contact of someone at high risk of syphilis, such as a male sexual partner who also has sex with men.[66] Anecdotal evidence suggests there may be limited implementation of risk screening due to the questions being outside the realm of antenatal care, particularly those regarding sexual history. Additionally, the risks related to partners and their sexual exposures may not be well known to the pregnant woman. The results of this study show that prior STI notification is a strong indicator of repeat syphilis infection, lending weight to the proposal that a history of STIs (syphilis, chlamydia or gonorrhoea) at any time can and should be used to identify women for additional screening in their third trimester and at birth, even in the absence of other identified risk factors. This criterion would be operationally feasible for midwives, does not require questioning about sexual history or sexual partners, and can be checked using existing medical records.

A study in São Paulo, Brazil, of a cohort of people treated in two reference centres for STI/AIDS between January 2004 and December 2012 identified 1,009 episodes of syphilis among 860 adolescents and adults, of whom 117 people (13.6%) presented with more than one episode of syphilis.[42] Male sex, MSM, HIV coinfection, and non-monogamous relationship were identified as risk factors for repeat infections. The proportion of repeat infections in this cohort is similar to that observed in the NSW general population cohort, with similar risk factors for reinfection. Although HIV status is unknown for the NSW cohort, given the NSW HIV context and the earlier study period of the Brazil study (partially prior to HAART), we expect HIV coinfection to play a bigger role in reinfection for that cohort.

A small study in Poland followed 54 MSM with first diagnosis of infectious syphilis between 2013–2016, with follow-up testing conducted every three months for two years or until the second episode of syphilis was diagnosed.[46] With this level of active surveillance, repeat infections were diagnosed in 12/54 (22%) of the cohort, higher than in the NSW general population cohort. A 2017 study of 323 MSM from San Francisco also identified reinfections in 22% of the cohort, with median time to syphilis reinfection of 24.9 months (approximately 756 days), much longer than the median time to reinfection for the repeat syphilis group in the NSW cohort.[67]

Two key factors consistently produced statistically significant increased hazard ratios in the model: being a man who has sex with men (MSM) and having a prior STI (chlamydia or gonorrhoea) notification in the 12 months to one month prior to a first infectious syphilis notification. These two factors are strong predictors of reinfection in first-time syphilis cases. As syphilis infections are concentrated in MSM populations the risk of sexual exposure within this cohort is compounded. A prior STI is a strong indicator of sexual risk exposure, and likely absence of STI prevention methods, such as condom use. Both factors can be used by health care professionals to indicate increased risk of syphilis reinfection and to target STI prevention messages and increased testing for these individuals.

The model identified a statistically significant effect modification between the MSM and prior STI variables, whereby overall risk of reinfection was slightly reduced for people who were both MSM and had a prior STI. The aHR of 0.36 should not be interpreted as an overall protective effect of this combination of predictors, but rather as a slight but statistically significant reduction in an already high risk for people with each of these predictors. This adjustment downwards in risk is likely attributable to the higher levels of health-seeking behaviour, engagement with sexual health services, and overall health care provision to men who are MSM, who are aware they are exposed to STIs, and who may take risk reduction measures such as more frequent testing or increased condom use.

This effect was also more likely to be detected due to the large number of people in the cohort who fell into the category of both yes to MSM and yes to prior STI, which increased the power and precision of the measurement.

Missingness of data has had a recurring impact on the model. The missing category is statistically significant for sex worker status (aHR 1.30, 95%CI 1.06–1.58, p=0.01), MSM (aHR 2.36, 95%CI 1.64–3.38, p<0.001), Indigenous status (aHR 0.72, 95%CI 0.56–0.92, p=0.01), and overseas born (aHR 0.59, 95%CI 0.49–0.71, p<0.001). With the exception the sex worker status, these results are all small but significant reductions in risk from the 'yes' category of each variable and indicate the likely heterogeneity in these groups. However, the overlapping confidence intervals between the 'yes' and missing categories in these variables also indicate the absence of a significant difference between the two groups.

## Prevention and mitigation strategies in NSW

STI prevention strategies in NSW have focused on MSM for more than two decades, leading to increased health-seeking behaviour among MSM and clinical awareness of the importance of sexual health services in these communities. Following outbreaks of syphilis among MSM in the UK, USA, and Europe prior to 2000, enhanced surveillance of positive syphilis serology commenced in NSW with enhanced data collection via the diagnosing clinician. The "Surveillance and Prevention of Sexually Transmissible Infections in Gay Men Action Group" (STIGMA) was formed in late 2000 as a partnership of public health units, sexual health researchers, GPs and community groups. STIGMA functions include monitoring patterns and trends in STIs among MSM and coordinating prevention and health promotion strategies.[68]

Websites such as Play Safe and Ending HIV offer reliable information about STIs, symptoms, testing and treatment, and connect users to sexual health services. Community and professional guidelines recommend routine STI testing for people living with HIV, and routine STI and HIV testing for MSM. National PrEP guidelines advise that clinicians should screen for STIs every 3 months in patients using PrEP.[69]

STI prevention and mitigation strategies include distribution of free condoms at many gay bars and at all sex-on-premises venues, and confidential assisted contact tracing services via websites such as Let Them Know (for all people), The Drama Downunder (for MSM) and Better to Know (for Aboriginal and Torres Strait Islander people). Health promotion materials targeted at MSM and Indigenous people raise awareness of STI symptoms and encourage prompt testing.

## Repeat syphilis and HIV

The review of the literature on syphilis and reinfection highlighted that HIV coinfection is an important consideration for syphilis reinfection. Due to privacy limitations HIV coinfection status has not been included in this study. The relationship between HIV infection and repeat syphilis infections is multilayered and has been influenced in recent years by development and expansion of HAART and PrEP. HAART allows people to lower their viral load to undetectable levels, which restores and supports immune function to allow a normal life span. PrEP decreases the risk of contracting HIV.

Many studies of syphilis infection and reinfection have focused on HIV-positive cohorts prior to the advent of HAART or with variable HAART uptake. These studies have shown that HIV-positive people have higher rates of syphilis infections and reinfections than HIV-negative people. The underlying reasons for this are varied and may include behavioural, clinical and immunological factors, such as immunosuppression due to untreated or poorly treated HIV infection leading to limited defence against *Treponema pallidum* infection.[22, 43, 67, 70-72] There is also evidence that syphilis infection increases the risk of HIV infection.[73, 74]

New South Wales has had great success in connecting HIV-positive people to effective treatment, with an estimated 99% of people with diagnosed HIV on treatment in 2020, and analysis by the Kirby Institute showing that 96% of these HIV-positive NSW residents on treatment have an undetectable viral load.[75] In this environment of very high HAART coverage and an overwhelmingly "Undetectable = Untransmittable" (U=U) population, the impact of HIV on syphilis reinfection in the study cohort is minimal.

### Syphilis increases the risk of HIV infection

A systematic review and meta-analysis of the effect of syphilis infection on subsequent HIV acquisition found that syphilis infection more than doubled the risk of HIV acquisition, compared with a control group.[73] There is evidence that syphilitic ulcers enhance the transmission of HIV by damaging the epithelial and mucosal barriers. *Treponema pallidum* and its constituent lipoproteins have been found to boost the transmission of macrophage-tropic HIV-1 via syphilitic lesions.[74]

### HIV coinfection, particularly in the absence of HAART, can make syphilis infections worse and harder to treat

Studies conducted before widespread HAART use showed that people with concurrent HIV infections were more likely to have multiple chancres (painless ulcers) at the primary stage, larger and deeper ulcers, more infectious lesions and a shorter incubation period.[72] HIV-positive people should be closely monitored for serological failure after syphilis treatment. A cohort study from China found that being

HIV-positive was associated with a 3-fold increased odds of treatment failure or reinfection after syphilis treatment.[22]

### Syphilis may reduce the effectiveness of ART – but evidence is unclear

There is some evidence that HIV and syphilis co-infection leads to increased plasma viral load and reduces the effectiveness of antiretroviral therapy (ART) for HIV-positive people, however, this must be interpreted with caution, taking into consideration the effectiveness of available ART at the time of the studies.[71, 76] Single-tablet ART regimens replaced multiple daily doses in 2006. This resulted in reduced side effects, which in turn decreased the necessity of regimen changes. Medication adherence improved, along with the quality and length of life of people living with HIV.

A slight and transient decrease in the CD4 cell count and an increase in viral load during syphilis infection has been observed in HIV-positive men, compared to HIV-positive men without syphilis.[77] ART uptake in this study cohort was 85%, but as the data collection period was prior to 2006, the effectiveness of this ART is not comparable to the ART used in the NSW cohort between 2014 and 2021.

More recent studies have examined syphilis and HIV coinfections specifically in the context of larger cohorts of people on effective HAART/ART and have shown no effect on viral load during syphilis infections. No statistically significant association between acute syphilis and risk of virologic failure was observed among a large cohort of MSM who were on ART and virologically suppressed at baseline between 2008 and 2015.[78] Newly diagnosed HIV-positive MSM with any STI (chlamydia, gonorrhoea, or syphilis) at baseline had higher median HIV RNA levels in blood plasma, seminal plasma and rectal secretions than those without STIs.[79] However, ART seemed to effectively suppress HIV RNA in all compartments in participants who adhered to the treatment, despite continuing high rates of STIs. This evidence supports the generalisability of the "Undetectable = Untransmittable" (U=U) message, regardless of STI coinfection.[80] However, the evidence of higher median HIV RNA levels in people with an STI before commencing ART does suggest that STIs may be an amplifying factor in HIV transmission in populations that are not using HAART.

### Links between HAART/PrEP use and STI incidence

The advent of HAART and the introduction of wider access to and uptake of PrEP have led to both 'risk compensation' (decreased condom use/changes in sexual risk taking behaviours), and increased rates of STI testing among users of PrEP, leading to better syphilis case ascertainment.[43, 65, 81-88]

In particular, recent evidence of a direct effect of PrEP use on STI incidence is limited and uncertain.[89, 90] A before-after analysis using a subcohort of the EPIC-NSW study found high but stable rates of STIs among high-risk MSM while taking PrEP, compared with a high but increasing trend in STI positivity

before commencing PrEP.[91] A similar study in Victoria with pre- and post-PrEP testing data found a small increase in incidence of STIs post-uptake of PrEP compared with pre-uptake of PrEP (Incidence rate ratio adjusted for change in testing frequency = 1.12, 95% CI, 1.02-1.23).[65]

## Limitations

### Data completeness and quality

A significant disadvantage of a retrospective cohort study design is the limited control the investigator has over data collection. The existing data may be incomplete, inaccurate, or inconsistently measured between subjects.

Risk data are collected via questionnaires sent to treating clinician by Public Health Units (PHUs). The completeness of data may be impacted by the health care providers' experience with syphilis, the volume of cases and questionnaires for the provider to assess and complete, and the capacity of PHUs to follow up on missing data.

Data quality and completeness around risk exposures may also be impacted by clinicians' understanding of the case's circumstances. Where a case does not disclose risk exposures such as PrEP use, sex work, or MSM sexual exposures, or a treating clinician does not explicitly ask about these, they are likely underreported.

RPR and VDRL tests are performed in different laboratories under different conditions over an extended period of time, and as such, some difficulties and errors of classification between continued and repeated infection are possible.

Movement of the cohort into or out of NSW during the study period is not captured. Individuals may have had a syphilis notification outside of NSW prior to their first notification in NSW or may have left NSW after their first syphilis notification and therefore their subsequent notifications are not included.

#### *Missing data*

The strength of this study has been impacted by missing data. Of the 9,171 notifications included in the study, 1,525 (16.6%) either had a missing value (1130/1525, 74.1%) for sexual exposure or had sexual exposure recorded as "unknown" (395/1525, 25.9%). Of the 8,572 notifications in males, 1,388 (16.2%) either had a missing value (1037/1388, 74.7%) for sexual exposure or had sexual exposure recorded as "unknown" (351/1388, 25.3%). I used this sexual exposure variable to create the MSM variable.

Taking the MSM variable as an example, the similarity in measures of effect and the overlapping confidence intervals between MSM 'yes' and MSM missing likely indicate that the MSM missing category in fact contains many true MSM 'yes' individuals. This observation is further supported by the

discordance in the MSM exposure variable over time for individuals with repeat notifications, whereby 34% of individuals with repeat syphilis who indicated no MSM exposure at first syphilis event went on to record MSM exposure at second syphilis event (Table 7). It is unlikely that all of these people had different sexual exposures between the two events, but probably points to data quality issues in the collection of this sexual risk exposure information at first event, either due to a reluctance to disclose the exposure to the health care provider, a false assumption made by the health care provider completing the enhanced surveillance form, or a reluctance of the health care provider to collect this information.

As seen in Table 2, at first notification, values for "Current sex worker" are missing for 24.9% of the cohort, values for "Country of birth" are missing for 30.3% of the cohort, and values for "Current PrEP user" are missing for 52.9% of the cohort. In the Cox regression analysis, the complete case analysis model is run on only 2,277 people out of a total cohort of 7,975. This tells us that, at enrolment in the study, 71.4% of the cohort had a value missing for one of the key variables of interest (PrEP use, sex worker, remoteness, indigenous status, country of birth, MSM exposure).

For sex work, it is possible that failure to disclose sex worker status indicates either unformalised or occasional sex work, and/or a lack of trust in the health care provider/patient relationship, that may translate into a less-thorough approach to risk mitigation for occupational exposures and poorer data collection and data quality for this group. The missing category of the sex worker status variable may in fact contain a number of people with sex work exposure. Disclosure of sex worker status and engagement with health care in this respect would provide a protective effect against repeat syphilis infections.

In the Cox regression analysis, model three was used specifically to address the volume of missing data in the PrEP use variable by excluding data from the first three years of the study period.

The PrEP use question entered the NSW Infectious Syphilis questionnaire in 2017, reflecting local access to PrEP from 2016 onwards following the advent of the EPIC study.[92] Any data entered prior to 2017 is retrospective (entered after 2017 against earlier cases) and may be of poor quality. On 1 April 2018 HIV PrEP became available through the Pharmaceutical Benefits Scheme (PBS), which subsidises the cost of medications for Australian citizens and permanent residents, leading to dramatically increased PrEP access and uptake. Following its listing, in 2018 7,410 people were dispensed HIV PrEP on the PBS for the first time in NSW.[93] To 31 December 2021 more than 51,800 people across Australia had ever been dispensed PBS-subsidised PrEP.[93]

### *Discordance in the MSM exposure variable over time for individuals with repeat notifications*

While some variability in sexual exposure history is to be expected over time within the cohort, an examination of the discordance between MSM exposure at first and subsequent notifications for people with repeat syphilis notifications reveals potential issues with data quality. Of the 973 individuals in the cohort with repeat notifications, 156 (16.0%) had their MSM exposure status recorded as either "no" or missing at first notification, but "yes" at their second notification (Table 7).

This discordance is particularly pronounced among those with their MSM status recorded as missing at first notification. Of these individuals, 133/197 (67.5%) had their MSM exposure recorded as "yes" at their second notification, suggesting that a significant proportion of those with MSM exposure missing at enrolment in the study (first notification) were in fact "yes" for MSM exposure. I cannot use imputation to fill the missing MSM exposure status at first notification because I do not have later notifications for the people in the single syphilis notification group to use for the same purpose.

These observations of likely data quality issues are further strengthened by examining a subset of the cohort with their MSM exposure status recorded as "no" at first notification and "yes" at third or later notification (Table 8). Of the six people with these values, five already had their MSM status recorded as "yes" by their second notification.

Table 7: MSM exposure status at first and subsequent notifications for individuals with repeat notifications (n=973)

| | MSM exposure status at notification 1 | | |
|---|---|---|---|
| | No n=68 | Yes n=708 | Missing n=197 |
| **MSM exposure status at notification 2 (%)** | | | |
| No | 35 (51.5) | 20 (2.8) | 13 (6.6) |
| Yes | 23 (33.8) | 559 (79.0) | 133 (67.5) |
| Missing | 10 (14.7) | 129 (18.2) | 51 (25.9) |
| **MSM exposure status at notification 3 (%)** | | | |
| No | 2 (2.9) | 4 (0.6) | 0 (0.0) |
| Yes | 6 (8.8) | 99 (14.0) | 42 (21.3) |
| Missing | 60 (88.2) | 605 (85.4) | 155 (78.7) |
| **MSM exposure status at notification 4 (%)** | | | |
| No | 0 (0.0) | 3 (0.4) | 0 (0.0) |
| Yes | 1 (1.5) | 10 (1.4) | 8 (4.1) |
| Missing | 67 (98.5) | 695 (98.2) | 189 (95.9) |
| **MSM exposure status at notification 5 (%)** | | | |
| No | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Yes | 1 (1.5) | 4 (0.6) | 1 (0.5) |
| Missing | 67 (98.5) | 704 (99.4) | 196 (99.5) |
| **MSM exposure status at notification 6 (%)** | | | |
| No | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Yes | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| Missing | 68 (100.0) | 707 (99.9) | 197 (100.0) |
| **MSM exposure status at notification 7 (%)** | | | |
| No | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Yes | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| Missing | 68 (100.0) | 707 (99.9) | 197 (100.0) |

Table 8: MSM exposure recorded over a series of notifications, individuals with repeat notifications and with MSM recorded as “no” at first observation, but “yes” at third or later notification (n=6)

| Cohort line | MSM1 | MSM2 | MSM3 | MSM4 | MSM5 | MSM6 | MSM7 |
|---|---|---|---|---|---|---|---|
| 125 | no | yes | yes | . | . | . | . |
| 661 | no | no | yes | . | . | . | . |
| 751 | no | yes | yes | . | . | . | . |
| 772 | no | yes | yes | . | . | . | . |
| 950 | no | yes | yes | yes | yes | . | . |
| 981 | no | yes | yes | . | . | . | . |

### *Observations on the collection of sex and gender data*

The NCIMS dataset records a variable called "gender" with values of male, female and transgender. There is no definition of transgender given in the enhanced surveillance questionnaire to guide GPs in completing the form, and it is not in line with updated reporting of sex and gender.

NSW is moving towards recording "sex assigned at birth" and "gender" as two separate data points. This improvement will allow us to make meaningful observations about the health of trans people in NSW. In its current format, this variable is not appropriate or useful to analyse.

I have reported on the category "transgender" in the descriptive analysis and retained it as a category in the Cox regression analysis for transparency about the dataset, however, I am not able to draw any conclusions about this group of people.

Without any understanding of their assigned sex at birth or their gender identity I have excluded them from the generation of the MSM variable and from any analysis of their sexual history or sexual exposures.

## Case ascertainment biases

As with most passive public health surveillance systems, case ascertainment relies on people with infectious syphilis getting tested. The case must present for testing and the treating clinician must order the test. Individuals in the reinfection cohort are only those who present for testing and are tested at subsequent infections. This is a limitation of using routine passive surveillance data to investigate reinfections. It is likely that the true number of Infectious Syphilis cases is higher than the number of notifications, and that the true proportion of reinfections is higher than the proportion of people with repeat notifications in the surveillance dataset.

### *Reinfections not identified due to absence of subsequent testing*

People with mild or no symptoms are less likely to be tested, and therefore less likely to be counted as cases. Some people with initial infections will have subsequent symptomatic infections that will not be detected by surveillance as these individuals do not re-engage with the health system and get tested at subsequent infections. These people may be a high-risk group for reinfections with unique risk factors, however, they are lost to follow-up in the cohort and not included in the reinfection analysis.

### *Higher rates of testing among people on HAART/PrEP*

People on HAART often undergo routine quarterly STI screening as part of their treatment, leading to higher rates of case detection.[88] The initiation of EPIC-NSW, a large-scale, targeted implementation study which rapidly rolled out PrEP to more than 9,500 individuals at high risk of HIV between March 2016 and April 2018, has led to increased rates of STI testing in NSW since 2016. Study participants

underwent HIV testing and STI testing every three months when they were dispensed PrEP for the duration of the study.[94] This increased rate of testing among people on PrEP will have increased case detection overall and disproportionately among MSM on PrEP.

Some users of on-demand PrEP do not have regular routine screening. Better data on testing and further research on the frequency of testing in high priority groups would inform the interpretation of case ascertainment biases in this respect.

#### Potential for case misclassification

Identification of reinfection is reliant on a correct classification and interpretation of the data by PHU and MoH staff. In the absence of laboratory evidence showing effective treatment for a prior infection, some reinfections may be misclassified as a continuation of an earlier infection. This may mean that the number of reinfections is underestimated in our dataset.

#### Exclusion of HIV status as a variable in analysis

HIV status is unknown for our cohort due to privacy limitations of the data available through NCIMS and the time limitations of this study which prevent data linkage of HIV status from other data sources. While the literature focuses on HIV as a significant risk factor for syphilis infections and reinfections, the majority of these studies are from overseas and pre-PrEP/HAART time periods with cohorts that are not comparable to NSW. New South Wales is recognised internationally for its advanced HIV response. Prevalence of HIV in NSW is very low, with the overwhelming majority of cases diagnosed and linked into effective treatment. With effective treatment on HAART and an undetectable viral load, the immunological profile of HIV-positive people in NSW is not a significant factor in syphilis infection and reinfection.

Risk taking sexual behaviours may remain a factor. A variable of 'Other STI Infection' (chlamydia or gonorrhoea) during the study period has been included to provide information about risk taking sexual behaviours.

### Generalisability

A strength of this study is the large cohort and length of study period, resulting in a large sample size and adequate time to capture reinfections in the cohort. Despite the inherent limitations of routine surveillance datasets, in particular their tendency to underestimate cases, they remain useful population-level sources of data on incidence and burden of infectious diseases such as syphilis. Surveillance data collection methods are largely static, which allows for stable comparisons over time and between systems. This study has good generalisability for other Australian states and territories

with similar population compositions and large metro populations, such as Victoria, ACT, and Queensland, and similarities in jurisdictional notifiable disease surveillance methods.

## Conclusions

This is the first study to quantify reinfection at population-level in NSW and indicates that >10% of infectious syphilis notifications are reinfections. The NSW reinfection incidence rate is lower than rates reported in high-risk groups internationally. Policies for prevention need to better consider the role of interventions to decrease rates of repeat diagnoses of sexually transmitted infections.

Enhanced syphilis surveillance data can improve targeting of syphilis reinfection prevention activities. In particular, evidence of prior STIs as a strong predictor of reinfection can be incorporated into guidelines such as antenatal screening. Data completeness and data quality impacted the analysis, with more than 70% of individuals missing values for at least one variable.

This study challenges some preconceptions held about the association of PrEP use and repeat syphilis notifications. The results shed light on the contribution of reinfection to the burden of syphilis in NSW and can inform the timing and prioritisation of targeted prevention activities.

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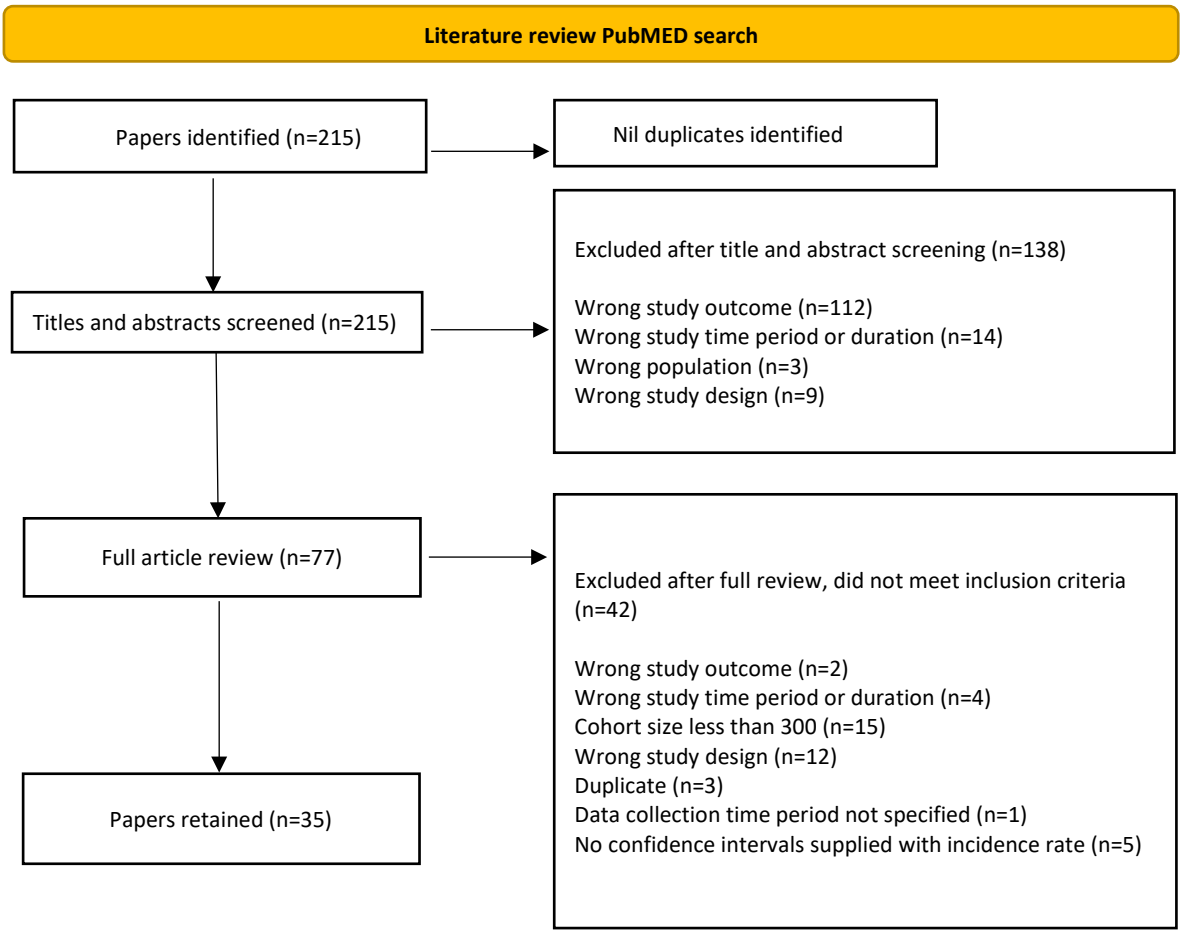
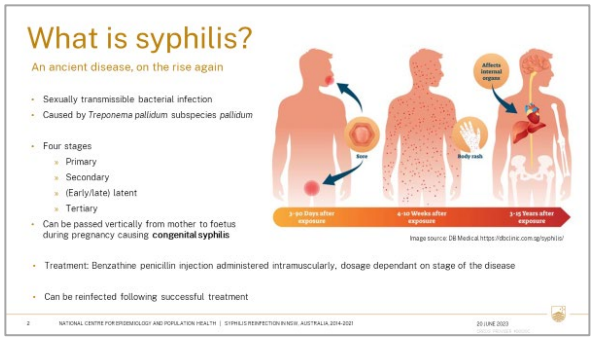
## APPENDIX A: Literature review search strategy

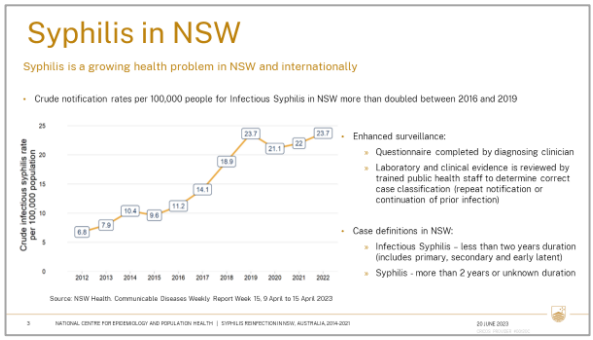
I conducted a literature review to contextualise my syphilis reinfection incidence rate result. I initially searched for papers specifically reporting reinfection incidence rates, however, there were very few of these, so I expanded my search to include initial and reinfection incidence rates. Many studies recruited their cohort either with no knowledge of prior syphilis infection, or with baseline syphilis screening that identified syphilis prevalence. Baseline syphilis infection usually did not exclude a person from the cohort study, meaning that incident infections during the study period could be first-ever syphilis infections or repeat infections.

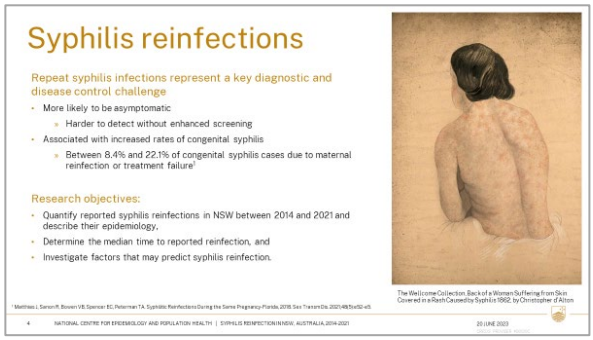
I searched the PubMED database for peer-reviewed papers. The search terms used were: “syphilis” AND “incidence rate” AND ("person years" OR "person-years" OR "PY"). The search was limited to English language papers published since 2009, with data collected from 2005. This was to capture incidence rate estimates from a roughly contemporaneous time period to our cohort. Studies with cohort sizes less than 300 people were excluded. Only cohort studies were included (retrospective or prospective). All references were imported into Rayyan. The original search returned 215 articles. There were no duplicates identified. 215 articles had their abstract and titles screened and 77 were retained for full article review. A further 42 were removed after full article review as they did not meet the inclusion criteria. The final number of articles retained was 35.

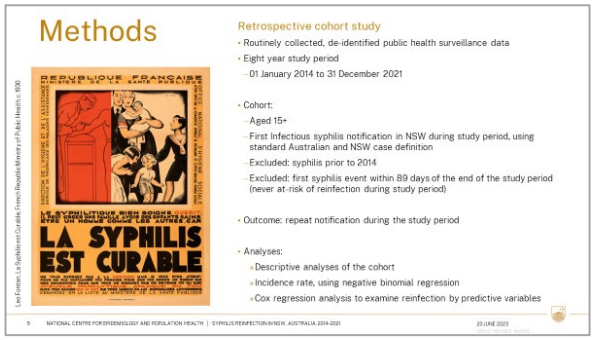


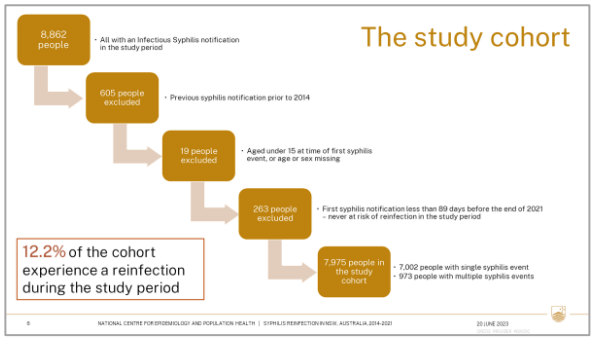
## APPENDIX B: Presentation slides from Communicable Diseases and Immunisation Conference, 20 June 2023

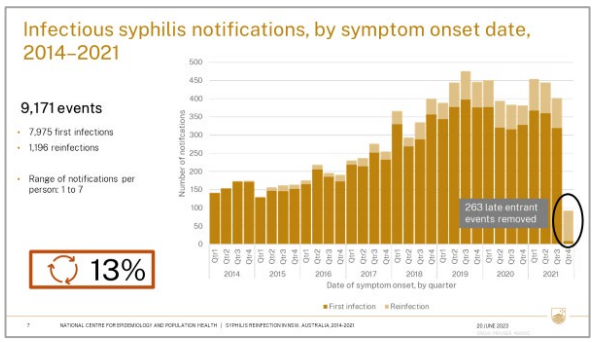



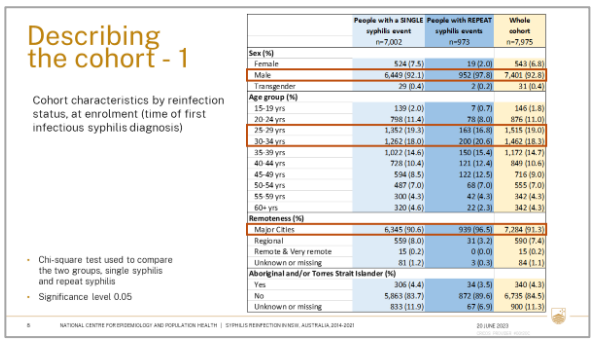




| | People with a SINGLE syphilis event n=7,002 | People with REPEAT syphilis events n=973 | Whole cohort n=7,975 |
|---|---|---|---|
| **Sex (%)** | | | |
| Female | 524 (7.5) | 19 (2.0) | 543 (6.8) |
| Male | 6,449 (92.1) | 952 (97.8) | 7,401 (92.8) |
| Transgender | 29 (0.4) | 2 (0.2) | 31 (0.4) |
| **Age group (%)** | | | |
| 15-19 yrs | 139 (2.0) | 7 (0.7) | 146 (1.8) |
| 20-24 yrs | 798 (11.4) | 78 (8.0) | 876 (11.0) |
| 25-29 yrs | 1,352 (19.3) | 163 (16.8) | 1,515 (19.0) |
| 30-34 yrs | 1,262 (18.0) | 200 (20.6) | 1,462 (18.3) |
| 35-39 yrs | 1,022 (14.6) | 150 (15.4) | 1,172 (14.7) |
| 40-44 yrs | 728 (10.4) | 121 (12.4) | 849 (10.6) |
| 45-49 yrs | 594 (8.5) | 122 (12.5) | 716 (9.0) |
| 50-54 yrs | 487 (7.0) | 68 (7.0) | 555 (7.0) |
| 55-59 yrs | 300 (4.3) | 42 (4.3) | 342 (4.3) |
| 60+ yrs | 320 (4.6) | 22 (2.3) | 342 (4.3) |
| **Remoteness (%)** | | | |
| Major Cities | 6,345 (90.6) | 939 (96.5) | 7,284 (91.3) |
| Regional | 559 (8.0) | 31 (3.2) | 590 (7.4) |
| Remote & Very remote | 15 (0.2) | 0 (0.0) | 15 (0.2) |
| Unknown or missing | 81 (1.2) | 3 (0.3) | 84 (1.1) |
| **Aboriginal and/or Torres Strait Islander (%)** | | | |
| Yes | 306 (4.4) | 34 (3.5) | 340 (4.3) |
| No | 5,863 (83.7) | 872 (89.6) | 6,735 (84.5) |
| Unknown or missing | 833 (11.9) | 67 (6.9) | 900 (11.3) |

## Describing the cohort - 2

Cohort characteristics by reinfection status, at enrolment (time of first infectious syphilis diagnosis)

| | People with a SINGLE syphilis event n=7,002 | People with REPEAT syphilis events n=973 | Whole cohort n=7,975 |
|---|---|---|---|
| **Country of birth (%)** | | | |
| Australia | 2,589 (37.0) | 441 (45.3) | 3,030 (38.0) |
| Overseas | 2,182 (31.2) | 350 (36.0) | 2,532 (31.7) |
| Unknown or missing | 2,231 (31.9) | 182 (18.7) | 2,413 (30.3) |
| **Men who have sex with men (MSM) (%)** | | | |
| Yes | 4,423 (63.2) | 708 (72.8) | 5,131 (64.3) |
| No | 1,343 (19.1) | 68 (7.0) | 1,411 (17.7) |
| Unknown or missing | 1,236 (17.7) | 197 (20.2) | 1,433 (18.0) |
| **Prior STI (365-30 days prior to first syphilis event) (%)** | | | |
| Yes | 1,456 (20.8) | 352 (36.2) | 1,808 (22.7) |
| No | 5,546 (79.2) | 621 (63.8) | 6,167 (77.3) |
| **Current sex worker (%)** | | | |
| Yes | 187 (2.7) | 19 (2.0) | 206 (2.6) |
| No | 5,095 (72.8) | 692 (71.1) | 5,787 (72.6) |
| Unknown or missing | 1,720 (24.6) | 262 (26.9) | 1,982 (24.9) |
| **PrEP user (%)** | | | |
| Yes | 785 (11.2) | 110 (11.3) | 895 (11.2) |
| No | 2,624 (37.5) | 241 (24.8) | 2,865 (35.9) |
| Unknown or missing | 3,593 (51.3) | 622 (63.9) | 4,215 (52.9) |

*MSM: Where sex was recorded as male and sexual history recorded either "Person(s) of the same sex only" or "Persons of both sexes."

** Prior STI: A gonorrhoea or chlamydia notification between 12 months and one month prior to first syphilis notification. This variable was designed to act as an indicator of sexual exposure risk behaviour

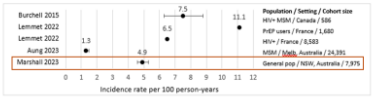


## Reinfection incidence rate

Overall incidence rate of reported reinfection across the cohort: **4.9 cases per 100 person years**

- Little published about syphilis reinfection incidence in general population cohorts – difficult to make comparisons
- Very limited understanding of syphilis reinfection at the broader community level
- Other syphilis incidence rates all calculated in high-risk populations, variation in study designs, many studies 10+ years ago

**Figure: Published reinfection incidence rates per 100 person-years, with 95% CIs where available, and information on study population, setting and cohort size. This study reinfection incidence rate included for context (Marshall 2023)**

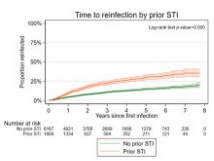


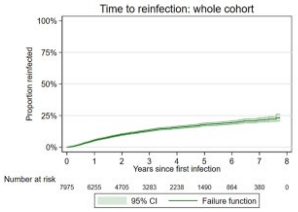



## Survival analysis - 1

Median time to reinfection impacted by low numbers of reinfections

- Kaplan Meier failure curves did not reach 50% reinfection in the study period
  - Male sex, MSM activity, Prior STI, Metro residence – all significant



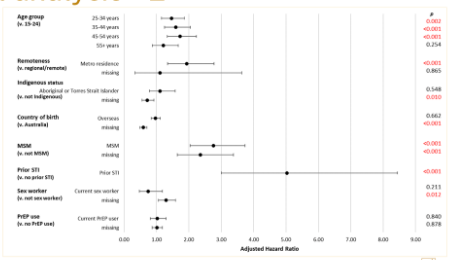






## Survival analysis - 2

Factors associated with reinfection

- **MSM exposure**
  aHR 2.76
  95 % CI 2.04–3.74
- **STI notification in the prior 12 months**
  aHR 5.03
  95% CI 3.00–8.44
- **Metro resident**
  aHR 1.93
  95% CI 1.34–2.78
- **Older age group**






## Limitations

### Data completeness and quality

- Data may be incomplete, inaccurate, or inconsistently measured between subjects
  - Completeness of data may be impacted by:
    - the health care providers' experience with syphilis,
    - the volume of cases and questionnaires for the provider to assess and complete, and
    - the capacity of PHUs to follow up on missing data.
  - Tests are performed in different laboratories under different conditions over an extended period of time

### Potential for case misclassification

- Some reinfections may be misclassified as a continuation of an earlier infection
  - Number of reinfections may be underestimated in our dataset

### Case ascertainment biases

- Reinfections not identified due to absence of subsequent testing
- Certain groups of people tested at higher rates


Image: Australian Government, Department of Health. Stop the rise of syphilis – Poster, 2021



## Summary

Syphilis infections are concentrated in males who reside in major metropolitan areas in NSW.

- 12.2% of cohort had reported syphilis reinfection
- Incidence rate 4.9 reported syphilis reinfections per 100 person-years
  - First calculation of incidence of reinfection in a general pop cohort
  - Lower than rates reported in high-risk groups internationally
- Predictors for reinfection: MSM exposure, prior STI
- HIV PrEP not associated with increased risk of syphilis reinfection

Enhanced syphilis surveillance data can improve targeting of syphilis reinfection prevention activities. In particular, evidence of prior STIs as a strong predictor of reinfection can be incorporated into screening guidelines, e.g. in antenatal settings.




# THANK YOU

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NSW Health

# CHAPTER 3

## Investigation of an acute public health problem or threat

Part A: The NSW public health response to the global mpox (monkeypox) outbreak

Part B: Investigation of a foodborne illness outbreak in the Nepean Blue Mountains Local Health District, NSW, November 2022

## Chapter 3: Table of contents

## List of abbreviations

| | |
|---|---|
| CDB | Communicable Diseases Branch |
| GP | General Practitioner |
| HIV | Human Immunodeficiency Virus |
| HPNSW | Health Protection NSW |
| LHD | Local Health District |
| MAE | Master of Philosophy (Applied Epidemiology) |
| MoH | Ministry of Health |
| MPX | Mpox (disease formerly known as Monkeypox) |
| MPXV | Monkeypox virus |
| MSM | Men who have sex with men |
| NBM | Nepean Blue Mountains |
| NCIMS | Notifiable Conditions Information Management System |
| NSW | New South Wales |
| NSWFA | New South Wales Food Authority |
| PCR | Polymerase Chain Reaction, a type of nucleic acid amplification test |
| PHU | Public Health Unit |
| PEP | Post-Exposure Prophylaxis |
| PrEP | Pre-Exposure Prophylaxis |
| SoNG | Series of National Guidelines |
| STI | Sexually transmitted infection |
| WGS | Whole Genome Sequencing |

## Preface

In this chapter I present two different experiences under the umbrella of investigating and responding to an acute public health problem or threat. I present my work on the NSW public health response to the global mpox outbreak, and a foodborne illness investigation that I conducted with a public health unit (PHU).

Together these experiences demonstrate all elements of the sub-competencies related to different aspects of outbreak investigation and response, including outbreak alerts, response, prevention, control, evaluation of the response, managing logistics, communications and report writing. Table A summarises how my cumulative outbreak experience meets the competency for MAE.

This chapter addresses the following competencies:

- Investigation of an acute public health problem or threat
- Prepare a manuscript for peer-reviewed publication (mpox)
- Conference presentation (Appendix A)
- Lay summary (Appendix B and Appendix C)

I arrived at NSW Health in the midst of a global response to an acute health threat. During my fourth week in field placement we marked the one-year anniversary of the WHO declaration of COVID-19 as a pandemic. NSW Health, like health systems around the world, was consumed by the response to COVID-19. In contrast to the United Kingdom, the country I had left just four weeks before I started MAE, NSW was an oasis of 'normal life' behind a fortress border. The Australian population had an expectation of a COVID-free life. Thousands of people worked in new systems of surveillance and quarantine, with seemingly limitless resources devoted to maintaining COVID-zero. We all waited for the salvation of vaccination. If we could just keep the prevention plates spinning in the air long enough, they would have time to lay down the vaccination pillows for a soft landing. Instead, in June 2021, Delta arrived in Sydney. The plates fell, and we learned that the pillows weren't as thick as we had hoped.

Like most MAE scholars, I expected to investigate a discreet foodborne illness outbreak for this chapter. A satisfying Cluedo where it's the coronation chicken sandwich filling in the canteen at the golf club. Gotcha! Or perhaps an interesting legionella cluster. Instead, my entire field placement has been on the frontlines of a series of public health responses to acute health threats, each too large, too critical, and too complex for one person to investigate or respond to: a life-changing global pandemic of a novel coronavirus; the first detection of Japanese Encephalitis in southern NSW; the first human cases of mpox ever recorded in Australia.

And that is the real lesson of this chapter: that public health is always about playing your part in a much bigger production. We train as field epidemiologists, we develop those analytical and investigative skills to respond to outbreaks, and then we deploy into a crowded and complicated environment where every part matters, from cleaners, to genomics experts, to the pig farmer who notices that something is not right with their animals. It is not a place for ego or individualism. No idea or solution, however brilliant, is formed or executed alone. Our ability to work at our tasks and fulfil our roles as part of a team is what makes us successful.

Don't worry, I did a foodborne illness investigation in the end.

## My role

I joined the monkeypox response about 24 hours after the first case was detected in NSW, on 18 May 2022. My first tasks were to participate in the first NSW expert panel discussion on management of the case and their contacts, and to support the Commonwealth Department of Health to draft the monkeypox SoNG by conducting rapid literature reviews of the infectious period and symptom profile of monkeypox. I also drafted the NSW factsheets for low-, medium-, and high-risk contacts.

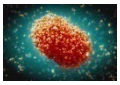
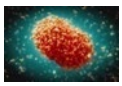
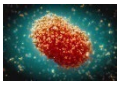
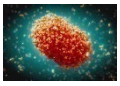
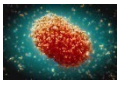
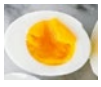
As the response developed, I prepared epi summaries and sitreps, presentation slides for NSW Infectious Diseases Network updates, drafted briefs to the Chief Health Officer and the NSW Health Minister requesting budget and approval to procure the JYNNEOS vaccine, managed correspondence with the public regarding mpox, and worked on the planning of the vaccination rollout. I drafted and distributed clinician alerts to GPs and hospitals.

In November 2022 I gave an oral poster presentation, "Once more unto the breach: The public health response of an Australian state to the global monkeypox outbreak 2022," at the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) online. I also presented Bug Breakfast on the epidemiology of and NSW public health response to mpox on 14 April 2023, to an audience of more than 280 people in the public health network in NSW.

I have written up the mpox outbreak response as a manuscript for submission to *Eurosurveillance* journal. With the focus of the outbreak in Europe and many other mpox outbreak response reports published in *Eurosurveillance*, we felt this would be a good choice of journal for this manuscript. If we are not successful, we will re-work the manuscript for *The Lancet Regional Health - Western Pacific*.

As part of my work with the Enterics team at Health Protection NSW I assisted the Nepean Blue Mountains public health unit (PHU) to investigate a foodborne illness outbreak linked to a high tea event at a hotel in the Blue Mountains in November 2022. This investigation allowed me to conduct an

Table A: MAE competencies for investigation of an acute public health problem or threat

| Competency | Monkeypox response | Foodborne illness investigation |
|---|---|---|
| Obtain preliminary information and describe:<br>• the nature of the problem, how it was discovered, the level of urgency to address it; and<br>• epidemiological and other data that has already been gathered. |  |  |
| Establish level of investigation and/or control necessary | Key emphasis on control, minor emphasis on investigation | Emphasis on both investigation and control |
| Define the objectives and scope of the investigation | |  |
| Design and conduct the field investigation | |  |
| Confirm the presence of an outbreak, and develop a case definition for initiating a descriptive epidemiological study | |  |
| Count cases and characterise the outbreak by time, place, person, and clinical and laboratory characteristics |  |  |
| Use this information to develop alternative hypotheses that include: likely aetiology (i.e. the pathogen), the cause (if not a pathogen), source, and risk factors for the outbreak |  |  |
| Test the hypothesis with an analytic study where appropriate (e.g. cohort or case control study) | |  |
| Assess the association between exposure and outcome, and consider causal association based on strength of association, dose-effect relationship, biological plausibility, and consistency of findings with other reports | |  |
| Identify, design, plan, and implement intervention control measures to prevent future recurrence of such outbreaks |  | |
| Evaluate the effectiveness of the control measures |  | |
| Write a report and recommendations |  |  |

outbreak investigation and apply the methods we were taught in course block. I followed the steps of an outbreak investigation and confirmed the outbreak by interviewing cases, established a case definition, tabulated and oriented the data by person, place and time, formulated and tested a hypothesis, conducted a cohort study and analyses, and communicated findings in the form of a report for the PHU and NSWFA. On this occasion the outbreak was self-limited and no control measures were required.

## Key reflections

### Mpox

Working on the mpox response honed my skills in managing competing priorities and, at times, conflicting opinions. Developing key response resources such as contact management guidelines early in the response, for a disease never before seen in Australia and about which little was known internationally was challenging enough, let alone doing it for a deadline of 'ASAP' and with input from various technical experts who didn't always agree with each other. There were continually new issues arising – what is our advice if a case has a pet dog? What is level of risk to a taxi driver if the passenger is wearing a mask? How do you notify a class of students that they are contacts of a mpox case without outing their teacher as MSM?

The successful response utilised many of our public health control measures: active case and contact management, engagement and two-way communication with clinicians and community groups, and targeted vaccinations. Each of these measures were developed over many years, they do not spring into existence when an emergency strikes. The experience of the COVID-19 response refined processes of case and contact management and developed a broad and highly skilled public health network in NSW, with staff in public health networks connected and able to provide surge capacity across the network at short notice. The network mobilised with the first case and collaborated to develop and share resources throughout the response. A long-standing relationship with ACON, a community-controlled HIV and LGBTIQ+ focused health promotion organisation founded at the height of the HIV/AIDS epidemic in NSW to advocate for community, allowed us to engage with affected communities and groups in partnership. ACON's leadership, reputation, and expertise allowed them to mobilise the community, deliver effective and accurate health messaging, and empower people to respond to mpox by taking charge of their health and reducing their risk of exposure. Behaviour changes such as reducing the number of partners, collecting contact information of sexual partners, and getting checked and tested if you develop symptoms are vitally important for controlling the spread of mpox. We were able to rapidly stand up a series of dedicated vaccination hubs and an online vaccination booking system because of prior investment in systems.

The preparatory work, the relationships, and the investment in systems, networks and upskilling are all developed over time long before they are required and enable a fast and successful public health response.

### Foodborne illness investigation

I started two foodborne illness investigations during my MAE. In late August 2022 the NSW Food Authority (NSWFA) received a complaint about a restaurant in the northern suburbs of Sydney, NSW. A large family group shared a meal at this restaurant on 6 August 2022, and eight of the 22 attendees at this meal later became ill with gastrointestinal symptoms. One of the sick people visited a GP on 13 August 2022 to seek treatment for diarrhoea and had a stool sample collected. This sample was run on a multiplex PCR for faecal pathogens and was positive for *Campylobacter spp*.

On 30 August 2022 the Northern Sydney PHU interviewed the *Campylobacter* case and gathered information about the food consumed by the group at the shared meal. The PHU decided that there was sufficient evidence to investigate further, with the aim to characterise the cases and identify the source of the infection, to inform any control measures and prevent future occurrences of disease. I joined the PHU on 31 August 2022 to conduct the investigation. My immediate actions were to create an outbreak questionnaire for Campylobacter and put it into REDCap. I sent the questionnaire to the case and asked them to distribute to other members of the dining party, as the case had preferred not to share details of the party due to cultural and linguistic concerns. And then I waited. And waited. And called the case again, with no response. After a week of no questionnaire responses and no reply to any attempt at contact, we accepted that the case had ghosted us and that was the end of the investigation.

By November 2022 I was wondering if I should give up, when another NSWFA complaint swung into view. This one lacked any specimens but made up for it with a very responsive cohort. I jumped on board. Despite the promising beginning, it was apparent following the initial investigations that, under normal conditions, this would not proceed. Sometimes you just need to make the best of what you have. The two foodborne illness investigation experiences delivered a wealth of learning. I applied the methods of statistical analysis of a cohort in an outbreak setting that we had been taught in course block. I calculated attack rates, risk ratios and I stratified. I calculated confidence intervals and p-values and had discussions with the OzFoodNet epi and others about the respective strengths and merits of each when determining measures of association. There is a move away from reliance on p-values, but they can still offer evidence, although they should not be interpreted in isolation.

I also gained experience in developing foodborne illness questionnaires using REDCap, and I was able to understand the limitations and real-world challenges of these kinds of investigations. These experiences will stand me in good stead in my public health career.

## Public health implications

### Mpox

Unlike countries in Europe and North America, Australia had relatively few cases of mpox and no evidence of sustained local transmission. The response leveraged prior experience, excellent relationships and networks, and the benefits of Australia's isolated geography. We had fewer introductions of the virus than other countries and we managed cases and contacts to control the spread of the virus. NSW administered more than 18,000 doses of vaccine in 14 weeks. The successful public health response is a case study in the control of a novel pathogen, and by publishing the outbreak response in an international journal we can share the experience and lessons in order to contribute to future outbreak responses.

### Foodborne illness investigation

A 2022 report by ANU, commissioned by the Food Standards Australia and New Zealand, estimated that foodborne illness and its sequelae costs Australia $2.44 billion every year, largely in lost productivity due to illness, together with premature mortality and healthcare costs.[1] Foodborne illness outbreak investigations are a crucial tool of public health and allow us to monitor the epidemiology of foodborne illness, identify threats, and take action to prevent harm. This outbreak investigation demonstrated the role of the Food Authority's complaint system to detect foodborne illness outside of notifiable conditions surveillance. This is an important case ascertainment route for foodborne illness.

## Acknowledgements

I am grateful to Robin Gilmour, Hayley Wareing, Holly Gibbons, and Valerie Delpech at Health Protection NSW for their support working on the mpox (monkeypox) outbreak in 2022. I acknowledge that the genomics analysis contained in the mpox manuscript is the work of Dr Rebecca Rockett, an author on the paper. Thank you to Rebecca for agreeing to contribute her expertise and for sharing her knowledge with me as we developed the manuscript. I am exceedingly grateful to Dr Anthea Katelaris, who has provided encouragement, advice, and supervision to me throughout my MAE, and in particular in the conception and development of the mpox manuscript. I also wish to thank Stephanie Wheeler and Amy Parry for helping me to present my multitude of outbreak experiences as one cohesive chapter.

Big thanks to Katherine Todd, Rachel Wilkins, and Adelaide Nyinawingeri at the Northern Sydney PHU for being great colleagues and teachers during my campy outbreak false start. They supported me to design my first outbreak questionnaire for campylobacter and helped me to put it into REDCap. Sadly it didn't work out for us an outbreak, but I loved the experience. Finally, thank you to Amanda Robinson at the Nepean Blue Mountains PHU for letting me jump into their foodborne illness complaint, and to Kirsty Hope for sharing her outbreak investigation expertise.

## Ethics

Ethics approval was granted by the Australian National University Human Research Ethics Committee under protocol 2017/909.

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# Part A: The NSW public health response to the global mpox (monkeypox) outbreak 2022

This draft manuscript has been prepared for submission to *Eurosurveillance* in the journal's outbreak report format, using the journal's specified section headings and the STROBE guidelines to structure the content.

**No evidence of sustained local transmission from imported cases of mpox (monkeypox) linked to global outbreak, New South Wales, Australia, May to December 2022**

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## Abstract

In May 2022, mpox cases with no travel history to endemic areas of Africa were reported across Europe and North America. In contrast to countries in Europe and the Americas, Australia has recorded relatively few cases of mpox. This report describes the demographic, clinical, and epidemiological characteristics of all 56 mpox cases notified in New South Wales (NSW), Australia's most populous state between 18 May and 31 December 2022, and the response to the outbreak coordinated by the NSW Public Health Network, comprised of staff in the Ministry of Health and public health units across the state. We report on outcomes of contact tracing activities, and results of phylogenetic analysis of 49 high-quality MPXV genomes generated from 33 mpox cases. We describe outbreak control measures, including successful community engagement and vaccination roll-out. Despite ongoing testing and surveillance we found no evidence of sustained local transmission in NSW and no secondary cases among known contacts.

## Background

Mpox (formerly monkeypox) is a disease caused by monkeypox virus (MPXV), a zoonotic Orthopoxvirus.[1] Mpox typically presents with systemic symptoms such as fever, headache, fatigue and lymphadenopathy, followed by characteristic rash or skin lesions.[2-4] Prior to 2003, human mpox cases were sporadic and limited to parts of west and central Africa.[5-7] In 2003 the first outbreak of mpox outside Africa was identified in the United States of America (USA); all 47 human cases had contact with pet prairie dogs that had been kept near small mammals imported from Ghana.[8, 9]

In 2017 a large outbreak in Nigeria highlighted a change in MPXV transmission dynamics from sporadic zoonotic spillover to human-to-human transmission.[10] Exportation of cases from the region, and subsequent human-to-human transmission to a healthcare worker in the United Kingdom (UK) in 2018 established a pathway by which mpox could spread from endemic to non-endemic regions.[11] Sexual transmission was identified as a possible transmission route in outbreak reports, together with clinical observations of genital lesions in a substantial number of cases.[10]

In May 2022, mpox cases with no travel history to endemic areas of Africa were reported across Europe and North America.[4, 12-21] Cases were reported almost exclusively among gay, bisexual, and other men who have sex with men. In contrast to countries in Europe and the Americas, Australia has recorded relatively few mpox cases from the beginning of the outbreak in May 2022 to the end of 2022. In particular, there has been no evidence of sustained local transmission in New South Wales (NSW), Australia's most populous state, home to 8.1 million people.

This report describes the characteristics of all mpox cases reported in NSW in 2022, and the response to the outbreak coordinated by the NSW Public Health Network.

## Outbreak detection

On 18 May 2022 a general practitioner in Sydney notified the local public health unit (PHU) of a suspected case of mpox in a man in his 40s. The patient presented with widespread painful lesions on his buttocks, the first of which appeared on 14 May, and also reported fever and lethargy. He had returned to Australia from Europe on 16 May and reported a history of sex with men, including visits to sex on premises venues, in France, Belgium, and the Netherlands in the two weeks prior to his onset.

Swabs were collected from the vesicular lesions and sent for urgent testing. Orthopoxvirus and MPXV DNA were detected by nucleic acid amplification testing (NAAT) and metagenomics recovered a complete MPXV genome within 24 hours, confirming this patient as the first case of mpox notified in NSW.

## Methods

Mpox became notifiable in NSW on 20 May 2022 with urgent public health priority, requiring health practitioners to notify their local PHU of clinically suspected cases in advance of testing. PHU staff must respond within 24 hours of notification to confirm appropriate testing, advise the suspected case to follow restrictions until a negative result is received, and, where there is a high index of suspicion, to identify contacts and assess their risk while waiting for test results.

We initially used guidelines from European countries and North America while we developed our own resources. National guidelines for surveillance and case and contact management were published in July 2022[22] and revised throughout 2022, with NSW-specific guidance produced to support implementation.

### Case definitions

Mpox cases are defined as either confirmed or probable based on the Australian national case definition.[23] A confirmed case was anyone with MPXV detected in a clinical specimen; a probable case was a person with clinically compatible symptoms and with detection of orthopoxvirus.

### Case interviews and data collection

All probable and confirmed cases notified in NSW between 18 May and 31 December 2022 were interviewed to collect demographic, clinical, and exposure information, including age, sex, sexual orientation, country of birth, symptoms, symptom onset date, prior smallpox vaccination, travel history, potential exposures, and possible place of acquisition. Information about the nature and extent of exposures to contacts was also collected to facilitate classification of low-, medium-, and high-risk contacts as per national guidelines and conduct contact tracing.[22] PHU staff and the treating clinicians remained in contact with all cases throughout their infectious period by telephone or automated text message. All data were entered into the confidential state-wide NSW Notifiable Conditions Information Management System (NCIMS).

Where cases reported no international travel during their exposure period, we investigated and interviewed all possible domestic upstream sources to determine if they had experienced any clinically compatible symptoms in the 21 days prior to their contact with the index case. Potential sources were offered serological testing to identify potential cryptic transmission; however, this was not mandatory.

### Laboratory diagnosis

Laboratory diagnosis was carried out initially using orthopoxvirus NAAT and whole genome sequencing (WGS), before MPXV-specific NAAT was developed and implemented. Specimens were collected from skin lesions, anorectal mucosa, throat and/or nasopharynx.[24] Samples where orthopoxvirus and/or MPXV DNA were detected were referred to the NSW Health Pathology – Institute of Clinical Pathology and Medical Research laboratory for WGS. Serological assays were available by August 2022 to investigate suspected mpox cases where MPXV DNA was not detected, potential asymptomatic or pauci-symptomatic infections and/or source contacts of cases, and antibody responses post-infection and vaccination. MPXV was also successfully isolated in Vero C1008 and buffalo green monkey cells.

### Contact tracing

All contacts were followed up based on their level of risk. Low-risk contacts were advised to monitor for symptoms for 21 days. Via NCIMS, medium and high-risk contacts were actively followed-up every three days or daily, respectively, for 21 days by telephone or automated text message surveys to check for symptoms and referral for clinical assessment if needed. High-risk contacts, and later medium-risk contacts, were assessed for, and offered post-exposure prophylaxis (PEP) vaccination, initially with ACAM2000™ vaccine and later with JYNNEOS® vaccine, where indicated.[25]

### Data sources

We extracted data on all NSW cases reported from 18 May until 31 December 2022 from NCIMS for analysis. We also extracted data on medium- and high-risk contacts of those cases, and cross-checked receipt of PEP vaccinations using the Australian Immunisation Register. We extracted data on the number of vaccine doses administered and the setting of administration from clinic records supplied to the NSW MoH. We received data from NSW Health Pathology on the number of samples tested for orthopoxvirus and/or MPXV NAAT and the percentage of those tests that were positive.

### Statistical analysis

Health-seeking delay was calculated in days from the date of symptom onset to the date of specimen collection, when the case received medical attention and mpox was suspected. Analyses were conducted in StataBE v17.0.[26]

## Results

### Cases

Between 18 May and 31 December 2022, 56 mpox cases were notified in NSW (Figure 1). All were male; the median age was 36 years (age range 26–55). Ninety-one percent (51/56) were residents of metropolitan Sydney. All cases reported same-sex sexual activity during their exposure period, prior to symptom onset. Six cases had known contact with a mpox case overseas or interstate, and four cases reported visiting sex on premises venues overseas.

Eighty-nine percent (50/56) acquired their infections overseas, predominantly in Europe (66%, 37/56); the most-visited country during the exposure period was Spain, followed by the UK, France, and the Netherlands. Two cases without international travel reported recent sexual exposures in a different state or territory within Australia. Four cases reported no international or interstate travel and acquired their infections in NSW from unknown sources.

Fifty-five percent of cases (31/56) were diagnosed via free public sexual health services and 32% (18/56) via primary care/general practitioner (GP). Eleven percent (6/56) were diagnosed via hospital emergency departments. The median time between symptom onset and clinical presentation was six days (range 1–21 days). Several cases reported noticing symptoms while abroad but delayed seeking testing or treatment until they returned to Australia, which contributed to longer health-seeking delays.

Figure 1: Confirmed and probable mpox cases by date of symptom onset (grouped by week) and place of acquisition, New South Wales, Australia, May–December 2022 (n=56).

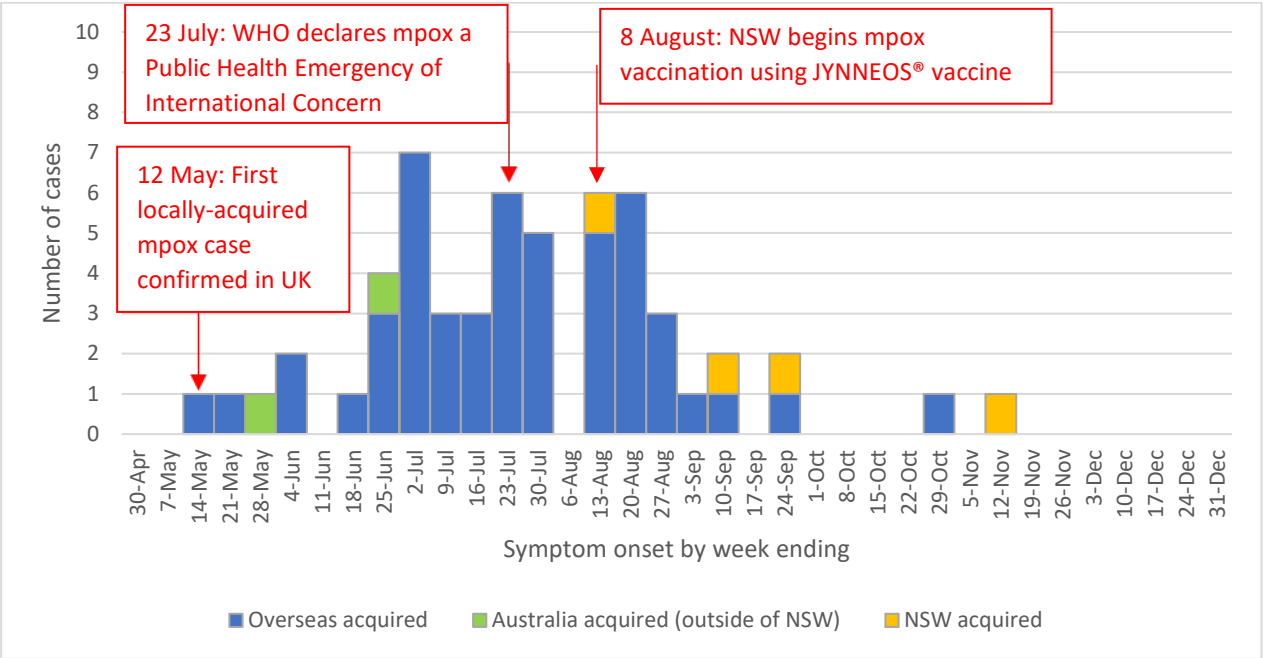



Table 1: Demographic and risk exposure characteristics of mpox cases, NSW, Australia, May–December 2022 (n=56)

| | | n | % |
|---|---|---|---|
| **Sex** | | | |
| | Male | 56 | 100 |
| **Age group (years)** | | | |
| | 25-29 | 12 | 21 |
| | 30-34 | 13 | 23 |
| | 35-39 | 18 | 32 |
| | 40-44 | 7 | 13 |
| | 45-49 | 2 | 4 |
| | 50-54 | 3 | 5 |
| | 55-59 | 1 | 2 |
| **Residence** | | | |
| | Metropolitan Sydney | 51 | 91 |
| | Outside metropolitan Sydney | 5 | 9 |
| **Country of birth** | | | |
| | Australia | 22 | 39 |
| | Overseas | 23 | 41 |

| | | | |
|---|---|---|---|
| | Missing | 11 | 20 |
| **Primary language** | | | |
| | English | 46 | 82 |
| | Other | 10 | 18 |
| **Sexual exposure** | | | |
| | Sex with men only | 53 | 95 |
| | Sex with men and women | 3 | 5 |
| **Known contact with mpox case** | | | |
| | Yes | 6 | 11 |
| | No | 50 | 89 |
| **Setting of diagnosis** | | | |
| | Sexual health clinic | 31 | 55 |
| | General practitioner | 18 | 32 |
| | Emergency department | 6 | 11 |
| | Interstate sexual health clinic | 1 | 2 |
| **Place of acquisition** | | | |
| | Overseas | 50 | 89 |
| | In Australia, outside of NSW | 2 | 4 |
| | NSW | 4 | 7 |
| **Continent of acquisition** | | | |
| | Europe | 37 | 66 |
| | North America | 9 | 16 |
| | South America | 4 | 7 |
| | Australia | 6 | 11 |

| **Recent travel, countries visited (some individuals visited multiple countries, count does not sum to 56)** | | | |
|---|---|---|---|
| Spain | 23 | Colombia | 3 |
| United Kingdom | 13 | Italy | 2 |
| France | 11 | Switzerland | 2 |
| Netherlands | 10 | Brazil | 2 |
| Germany | 7 | Israel | 2 |
| Greece | 7 | Singapore | 2 |
| USA | 7 | Turkey | 2 |
| Canada | 3 | | |

All cases except one had a rash or skin lesions and 64% (35/55) reported lesions on their buttocks and/or anogenital region (Table 2). Eleven percent (6/56) of cases reported no systemic symptoms.

The most reported systemic symptom was fever (65%, 36/56 cases) followed by lymphadenopathy (43%, 24/56), headache (27%, 15/56), and muscle pain (25%, 14/56).

Five cases required hospital review, of whom three were admitted for inpatient clinical care: one for additional sampling and clinical review; one for secondary bacterial infections and pain management, and one for perirectal pain and concerns for a perirectal abscess. Two cases were referred with ocular complications, and one of these cases was prescribed Tecovirimat. There were no deaths. Cases requiring hospital assessment and admission were referred to the NSW Biocontainment Centre, a specialised facility with protocols for the management of high consequence infectious diseases. Where necessary, cases and contacts were also referred to the Special Health Accommodation, a quarantine and isolation facility established during the COVID-19 response, when they were unable to isolate or stay in their usual residence.

Table 2: Clinical characteristics of mpox cases, NSW, Australia, May–December 2022 (n=56)

| | | n | % |
|---|---|---|---|
| Rash or lesions | | | |
| | Yes | 55 | 98 |
| | No | 1 | 2 |
| If yes to above, rash or lesions on the buttocks or anogenital region | | | |
| | Yes | 35 | 64 |
| | No | 14 | 25 |
| | Unknown or missing | 6 | 11 |
| Other symptoms | | | |
| | Fever | 36 | 65 |
| | Lymphadenopathy | 24 | 43 |
| | Headache | 15 | 27 |
| | Muscle pain | 14 | 25 |
| | Fatigue or malaise | 13 | 23 |
| | Anorectal pain | 8 | 14 |
| | Cough or sore throat | 7 | 13 |
| | Joint pain | 6 | 11 |
| | Back ache | 6 | 11 |
| | Runny nose / nasal congestion | 2 | 4 |
| | Painful or difficult urination | 1 | 2 |
| | Eye pain | 2 | 4 |
| | Night sweats | 1 | 2 |

## Contacts

*Contact demographics*

We identified 31 high-risk and 81 medium-risk contacts of the 56 cases. Similar to cases, the majority of contacts resided in metropolitan Sydney, including all high-risk contacts. High-risk contacts were predominantly male (87%, 27/31) and ranged in age from 2–63 years. Twenty-seven (87%) were household contacts, including 13 sexual partners and 14 other household contacts. Of the four non-household high-risk contacts, three were sexual contacts and one was exposed while working as a massage therapist. No healthcare workers were classified as high-risk contacts from occupational exposures.

*Contact management with post-exposure prophylaxis*

All high-risk contacts were risk assessed and considered for PEP at all phases of the response. Of the 14 high-risk contacts notified prior to availability of JYNNEOS® vaccine, only one was given ACAM2000™ PEP. Two contacts reported smallpox vaccination as a child. Eleven of 17 contacts (65%) received PEP with JYNNEOS® after it became available. The reasons given for not receiving PEP included: declined (n=3), too long after exposure (n=2), and risk-benefit not considered in favour for an infant (n=1). None of the six high-risk contacts who did not receive JYNNEOS® PEP were sexual contacts of a case. Once JYNNEOS® supply was less constrained, medium-risk contacts were also offered PEP vaccination where indicated.

*Contact outcomes*

There were no secondary infections in any contacts notified in NSW, and no known transmission in NSW from locally notified cases. However, on three occasions, both partners in a couple were notified as mpox cases at the same time. There were also two co-travelling groups where three people in each group were diagnosed with mpox. In each of these situations, it was not possible to tell if they had a common exposure source, or if one case had infected the other(s).

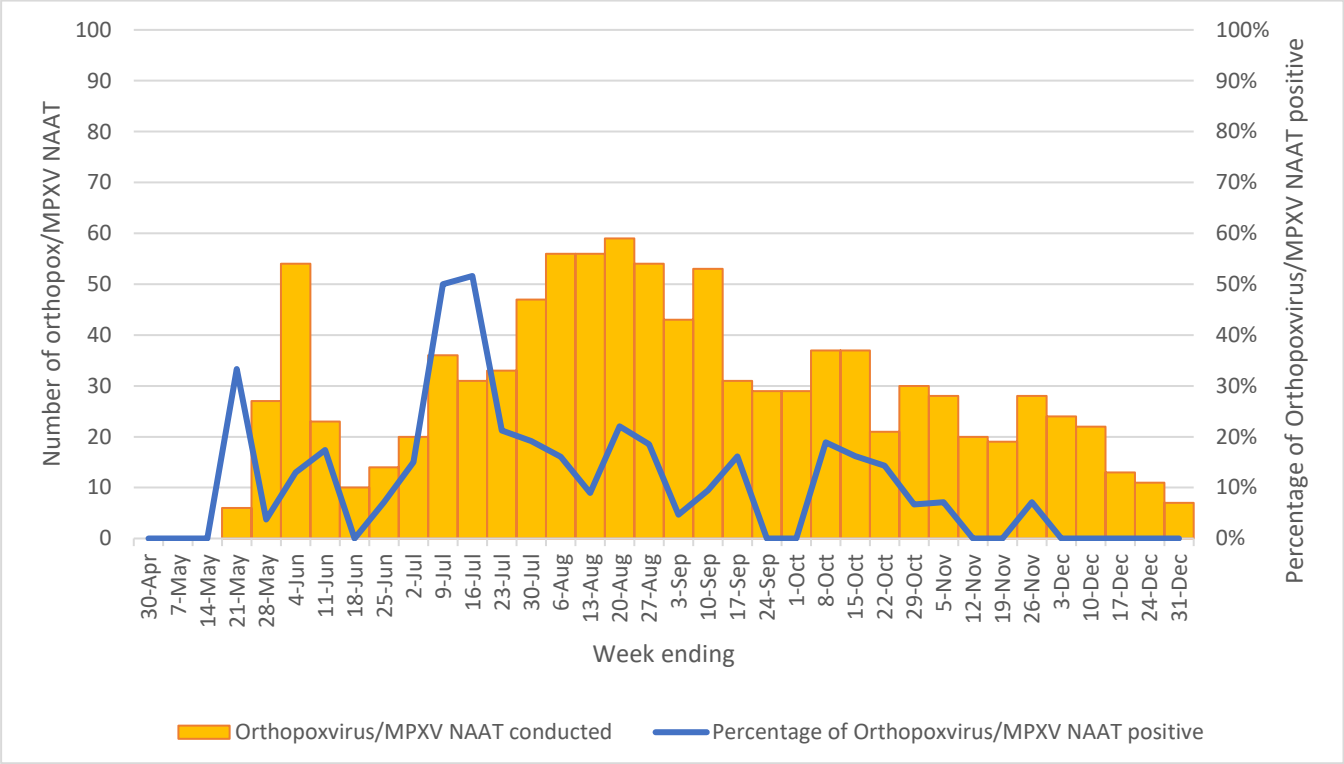
## Exposure investigations – locally-acquired

All identified potential sources of locally-acquired infections were interviewed to assess recent symptoms, overseas travel or other exposure risk factors. Three upstream contacts of two locally acquired cases underwent serological testing to determine if they had evidence of previous mpox infection (none had received vaccination). No MPXV antibodies were detected in the three contacts.

### Laboratory investigations

Mpox testing requests peaked in August 2022 (Figure 2). As case numbers declined there was a corresponding decrease in the number of NAAT conducted. The test positivity rate peaked between 10 and 16 July 2022 at 52%.

**Figure 2: Number of samples tested for orthopoxvirus and monkeypoxvirus by NSW Health Pathology and the positivity rate*, May–December 2022. Data source: NSW Health Pathology.**




* Positivity rate is based on specimens tested, not individuals. Many individuals have multiple specimens tested. Positivity rate is calculated as number of positive orthopoxvirus or MPXV NAATs/number of positive and negative orthopoxvirus or MPXV NAATs per week.

WGS was attempted on 86 clinical specimens collected from 48 cases where orthopoxvirus or MPXV DNA was detected; and 49 high-quality MPXV genomes (>98% genome coverage, mean read depth >50x) were generated from 33 cases. Phylogenetic analysis of these genomes showed that all NSW cases were contained within the 2022 outbreak clade IIb sub-lineage B.1 (Figure 3A), with limited genomic diversity. For nine cases, multiple specimens (median = 2, range 2-6) were available for genomic analysis (Figure 3B). In most cases swabs were collected from multiple vesicles at the same time, two cases had specimens collected 1 and 8 days apart. Intra-host diversity was noted in four cases demonstrating up to 7 single nucleotide polymorphisms (SNPS) between MPXV genomes collected from the same patient (mean 0.72 SNP, range 0-7) (Figure 3C). These findings support other

reports describing microevolution within mpox vesicles.[27] We also investigated four pairs (three couples and one pair of travelling companions), who all became infected with MPXV to determine if MPXV genomic diversity would support MPXV transmission between each pair. Between two and six SNPs were detected between these four pairs, compared to an average of 2.3 SNPs (range 0-8) between unlinked NSW cases and the B.1 outbreak reference genome (Figure 3B and 3C). The low genetic diversity and microevolution between vesicles detected in our analysis limits attempts to use genomics to support epidemiological investigations to identify transmission of MPXV.

Figure 3: Phylogenetic analysis of mpox cases in NSW, May–December 2022. Data source: NSW Health Pathology.

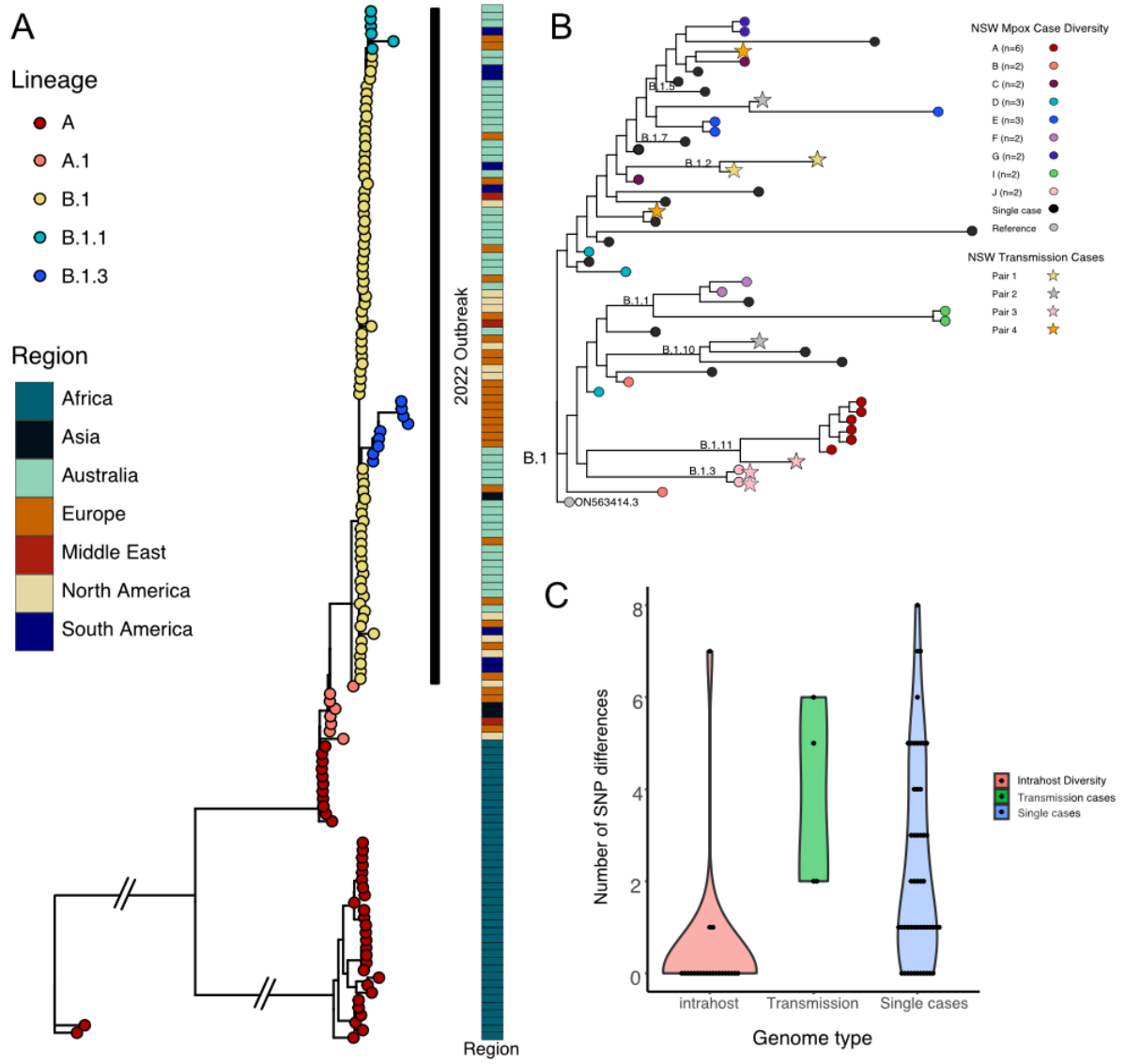



Figure 3A. Maximum likelihood phylogeny of 138 international MPXV genomes, including 33 mpox cases from Australia during the 2022 outbreak. All NSW genomes (n=49) were contained within the clade IIb sub-lineage B.1 with limited diversity compared to B.1 outbreak genomes from Europe, North and South America, Asia and the Middle East. MPXV lineages with less than 5 cases (A.1.1 (n=1), A.2 (n=1), B.1.2 (n=4), B.1.4 (n=3), B.1.5 (n=2), B.1.6 (n=2), B.1.7 (n=4), B.1.8 (n=1)) have been collapsed.

3B. The phylogeny from NSW cases demonstrates the genomic diversity of lineage B.1 MPXV genomes detected in NSW. Nine cases where multiple MPXV genomes were obtained from the same individual are highlighted with coloured nodes. Four couples that are likely transmission pairs are indicated with star nodes. These results demonstrate microevolution between different mpox vesicles from the same patient and transmission pairs.

3C. Violin plot of single nucleotide polymorphisms (SNP) between MPXV genomes obtained from the same case (pink), between likely transmission pairs (green) and between the reference genome and MPXV genomes from cases without epidemiologically defined transmission links (blue). Up to 7 SNP between the MPXV genomes obtained from the same patient were identified and two to six mutations were detected between the four likely transmission pairs.

## Outbreak control measures

**Community engagement**

From early May, we worked closely with several community organisations and sexual health services to deliver accurate and appropriate health messages to priority groups and to organise and promote targeted vaccination based on agreed risk criteria. The Sex Workers Outreach Project (SWOP) provided outreach peer education to sex workers, while the Bobby Goldsmith Foundation and Positive Life NSW played an instrumental role in the provision of health promotion advice for people living with HIV (PLHIV).

LGBTIQ+ community health organisation ACON used its leadership and strong reputation in the HIV and LGBTIQ+ communities, built over several decades of engagement and advocacy, to mobilise rapidly to develop and deliver mpox awareness, testing, and risk reduction messaging. Their expertise in community mobilisation, social marketing, and online engagement strategies allowed them to facilitate the rollout of the vaccination campaign. ACON also provided peer support at vaccination hubs and held two community forums to connect clinical and public health staff with affected communities.

**Case management and contact guidelines**

During the height of the outbreak, we held daily case review meetings to discuss cases and contact management. The frequency of these meetings reduced to twice weekly, and eventually ceased in the absence of new case notifications.

Contact definitions and management changed over the course of the response. Initially contacts from workplace settings were classified as high-risk, but later these were assessed as medium- or low-risk, depending on duration and nature of contact. In the first two months of the response we contact traced case flights but ceased this in August 2022 in line with updated guidelines and in the absence of evidence of in-flight transmission. Early contact tracing also involved identifying taxi and ride-share drivers who drove cases. These drivers were classified as low risk. Due to limited evidence for respiratory droplet transmission in short duration car rides, potential privacy breaches, and the additional burden on public health staff, this practice was terminated in August 2022.

**Vaccination**

In May 2022 the only smallpox vaccine available in Australia was ACAM2000™, a second-generation vaccine containing replication-competent live attenuated vaccinia virus. The third-generation smallpox vaccine, a replication-deficient modified vaccinia Ankara (MVA) vaccine supplied under the product name JYNNEOS®, was not approved by the Australian Therapeutic Goods Administration

(TGA) and therefore not licenced for use in Australia. In May 2022 the TGA made JYNNEOS® available under an emergency use provision of the Therapeutic Goods Act 1989.[25]

We estimated 45,000 doses of JYNNEOS® in a two-dose schedule would be required to vaccinate those at highest risk of acquiring mpox in NSW. Due to constraints on global vaccine supply, NSW was only able to secure 5,500 vials of vaccine for the first phase of the vaccination program. Priority vaccination criteria included men who have sex with men (MSM) on pre-exposure prophylaxis for HIV (PrEP), sexually active MSM who are immunocompromised or living with HIV, sex workers who had MSM as clients, and MSM with international travel booked to regions with known mpox outbreaks. Laboratory staff and healthcare workers at higher risk of exposure to mpox were also prioritised for vaccination.

Together with ACON, we operated an online system that enabled people seeking vaccination to determine their eligibility according to prioritisation criteria and submit an expression of interest. These lists were reviewed by clinicians and eligible people were sent an online vaccine booking link. Vaccination clinics also contacted eligible people to book them in where required.

On 8 August 2022 NSW commenced JYNNEOS® vaccination via subcutaneous injection. We established a dedicated temporary mpox vaccination hub in inner metropolitan Sydney to meet the demand for vaccination among eligible MSM. Additional approved vaccination sites included selected specialist primary care clinics that prescribe antiretroviral treatment and care for PLHIV, and publicly funded sexual health or community health clinics.

Further JYNNEOS® doses became available later in August and additional vaccine hubs across metropolitan Sydney opened. Hubs prioritised key populations such as sex workers, Aboriginal and Torres Strait Islander people, and trans and gender-diverse people.

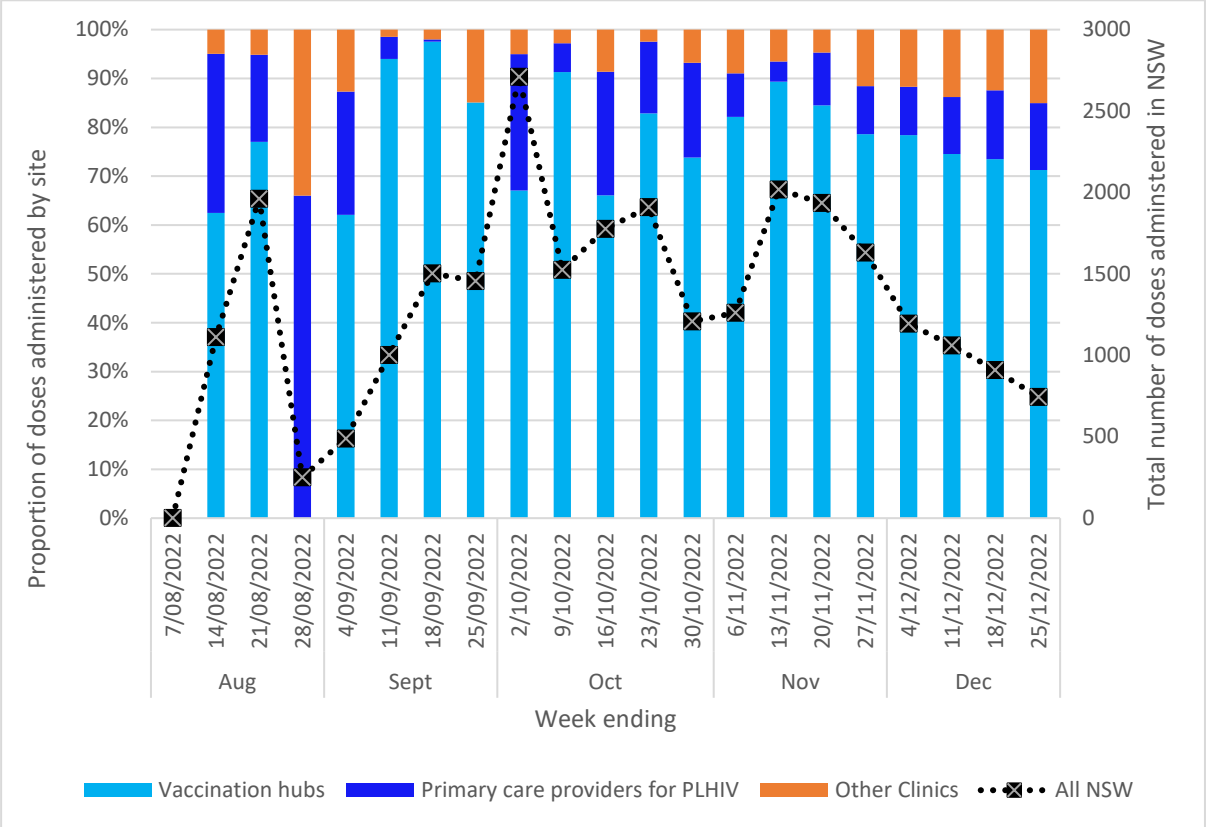
In response to the ongoing limited vaccine supply and in line with global changes in recommendations for vaccine administration route, on 5 September 2022 NSW switched to intradermal administration. Intradermal vaccination allowed for dose saving, by extracting up to five doses from a single vial, rather than administering a full vial per dose subcutaneously.[28] There were also anecdotal reports of a reluctance towards intradermal administration due to concerns about obvious injection site reactions and/or keloid scarring, and the potential stigma of being identified as having received mpox vaccine. This issue was partially mitigated by offering intradermal administration in the deltoid rather than the forearm.

The switch to intradermal administration and additional supplies of vaccine permitted an expansion in vaccination eligibility to include all MSM and anyone of any gender who has sex with these men. By October 2022, a purpose-built state-wide online booking system streamlined access to vaccination

and additional vaccination sites opened across regional and rural NSW. On 12 January 2023, with vaccine supplies stable, NSW reverted to subcutaneous administration.

Between 8 August and 31 December 2022 we administered 27,659 doses of JYNNEOS®; 68% of people vaccinated received a second dose. Vaccination hubs administered 71.3% of doses, followed by sexual health clinics (15.0%) and primary care/GPs (13.7%) (Figure 4).

**Figure 4: Total number of JYNNEOS® vaccine doses administered in NSW (black dotted line), and breakdown of doses by setting of administration, by week ending, 1 August to 25 December 2022.**




## Discussion

In contrast to countries in Europe and the Americas, Australia has recorded relatively few cases of mpox. There has been no evidence of sustained local transmission in NSW and no secondary cases among known contacts. We credit the success of the response to several factors. Firstly, we utilised established close working relationships between public health staff and clinicians to share information, enhance case detection, and facilitate the vaccination roll-out. Secondly, the response centred around the gay, bisexual and MSM community and actively partnered with community health organisations to rapidly develop and deliver appropriate and acceptable mpox awareness, testing, and risk reduction

messaging. Proactive risk reduction behaviour by affected communities have been reported in the USA,[29] and anecdotally we understand similar actions were taken by gay, bisexual and MSM in NSW.

Thirdly, we were able to enact early and active contact management through the public health workforce, highly skilled secondary to the COVID-19 pandemic. Fourthly, recent experience developing systems for mass COVID-19 vaccination permitted a rapid roll-out of targeted vaccinations. Increasing coverage in high-risk groups from August 2022 likely contributed to the lack of transmission among contacts. This is supported by recent estimates of real-world vaccine effectiveness of JYNNEOS® which range from 75.2% to 35.8% for single-dose vaccination and 85.9% to 66.0% for two-dose vaccination.[30, 31]

Finally, it is likely that Australia's isolated geography played a role in limiting the number of mpox introductions into the NSW community and allowing the public health response a 'head start'. Arrivals and departures data show that movements between May and August 2022 were only 50% of pre-pandemic levels observed prior to 2020.[32] By September 2022 global mpox case counts were plummeting, and continued to decrease dramatically until the end of our study period, thus reducing the risk of mpox introductions into the NSW community.

Some of the challenges of the response were the limited and inconsistent vaccine supply, and complications related to the switch to intradermal administration. Stigma related to disease transmission through predominantly MSM sexual networks presented a set of particular challenges. These included contact tracing while maintaining the privacy of cases in workplace or educational settings, reluctance of some cases to engage with public health investigations, and balancing the need to provide accurate public messaging about at-risk populations without perpetuating stigma.[33] Widespread use of "hook-up" apps which allow anonymity for sexual partners made contact tracing difficult in some circumstances.

There are several limitations to our study. Data have been collected for the purposes of surveillance and case and contact management and may not have been collected consistently. The small sample size may make the results less generalisable. While we report no evidence of sustained local transmission, we acknowledge that four cases acquired their infections in NSW from unknown sources, and so we cannot rule out local transmission undetected by our surveillance system. However, the lack of large numbers or clustering of locally acquired cases, together with ongoing surveillance and sustained testing, suggests that the amount of undetected transmission was likely to be small.

Looking to the future, there is more to learn about the control and prevention of mpox to improve our global response. The nature and duration of protection offered by vaccination requires ongoing

analysis. Whether vaccination prevents transmission or attenuates disease severity, and how many doses of vaccine offer adequate protection remains to be determined. Further research is needed to understand the role and potential integration of mpox screening and vaccination into routine sexual health services and guidelines, including HIV pre-exposure prophyalxis prescribing guidelines and care for PLHIV.[34]

## Acknowledgements

We would like to thank the cases and contacts for their cooperation and openness with public health staff. We also acknowledge the work of clinicians, particularly sexual health services and general practitioners, who are the first point of contact for mpox cases and are vital to the success of the response. We acknowledge the work of staff across NSW public health units, NSW Health Pathology, the Westmead Institute of Medical Research, the Centre for Infectious Diseases and Microbiology – Public Health, and the Clinical Excellence Commission.

We thank all staff from Health Protection NSW and the Centre for Population Health, NSW Ministry of Health. Special thanks to Angela Brown from eHealth at the NSW Ministry of Health who built the vaccine booking system, and to Sonya Ennis and Mareeka Hair from the Immunisation team in Health Protection NSW who led the procurement, storage and distribution of the JYNNEOS® vaccine.

## Ethical statement

Ethics approval for this investigation was not required as it was undertaken for health protection purposes under the provisions of the *Public Health Act 2010 (NSW)*. All data have been collected by routine public health surveillance systems and Ministry of Health activity reporting systems. No additional data have been collected for research purposes.

Ethics approval for outbreak investigation and publication by the MAE Scholar was granted by the Australian National University Human Research Ethics Committee under protocol 2017/909.

The authors report no conflicts of interest.

## Informed consent

No personal identifiable data for cases are included in this report.

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## APPENDIX A: Poster presentation at European Scientific Conference on Applied Infectious Disease Epidemiology, 23 November 2022

# Once more unto the breach: The public health response of an Australian state to the global monkeypox outbreak 2022

Justine Marshall[1], Robin Gilmour[2], Valerie Delpech[2], Md Rezanur Rahaman[1], Jeremy McAnulty[2]

**In contrast to countries in Europe and North America, Australia has recorded relatively few cases of monkeypox. In particular, there has been no evidence of sustained local transmission in the most populous state, New South Wales.**

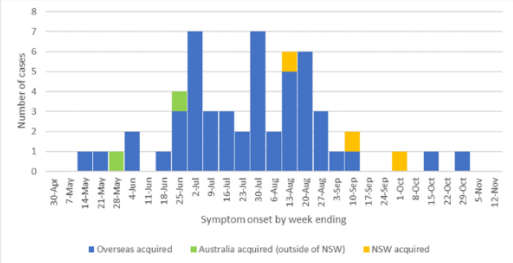


Figure 1: Monkeypox case notifications in NSW, by week of symptom onset, 1 May to 12 November 2022

The success of the response is due to:

- active case & contact management,
- early and targeted vaccinations,
- proactive behaviour change by affected communities to reduce their risks, and
- Australia's isolated geography, which has limited monkeypox introductions.

We must continue to work with priority communities to maintain awareness of risk and prevention measures, and access to and uptake of vaccination, as we approach the WorldPride event in Sydney in February 2023.

## Introduction

Monkeypox is a zoonotic virus. Prior to 2022 it was associated with exposure to infected animals, primarily in Central and West Africa.

| | |
|---|---|
| May 2022 | Monkeypox cases reported across Europe and North America; cases have no travel history to endemic areas of Africa. |
| 18 May | First case of monkeypox in New South Wales (NSW) detected in a man aged in his 40s who had recently returned from Europe. |
| 20 May | Monkeypox notifiable in NSW. |
| 23 July | WHO declared the escalating global outbreak a Public Health Emergency of International Concern. |
| 26 July | Australia's Chief Medical Officer declared the outbreak a Communicable Disease Incident of National Significance. |
| 8 August | NSW commenced vaccination using the third generation smallpox vaccine. |

## Methods

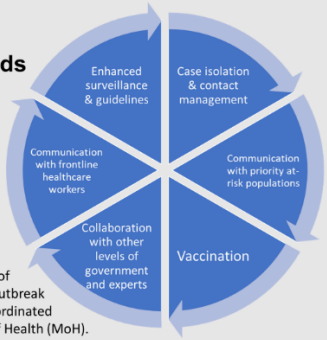


Figure 2: Components of monkeypox outbreak response, coordinated by Ministry of Health (MoH).

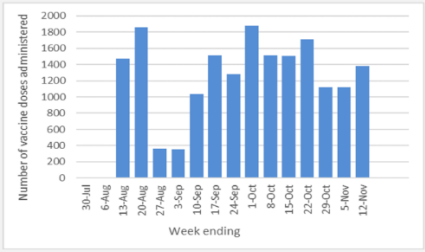


Figure 3: Jynneos vaccine doses administered in NSW, by week ending, 8 August 2022 to 12 November 2022

## Results

To 12 November 2022 NSW has detected **55 cases** of monkeypox.

All are male, median age 36 (range 26-55). Most cases report same-sex sexual activity prior to illness.

33 high-risk and 63 medium-risk contacts have been identified. There have been no secondary infections from known cases identified in NSW, although three cases have acquired their infections in NSW.

18,097 doses of vaccine have been administered since 8 August 2022.

From early May, MoH worked closely with ACON, an HIV and LGBTIQ+ focused health promotion organisation, and sexual health services to deliver accurate and appropriate health messages to priority groups and to organise and promote targeted vaccination based on agreed risk criteria.

Justine is completing the Australian Field Epidemiology Training Program, MPhil in Applied Epidemiology (MAE program), in infectious diseases at Health Protection NSW.

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## APPENDIX B: Mpox clinical alert, 8 August 2022

# MONKEYPOX

*Information for clinicians – Please distribute to Emergency Departments, Sexual Health Services, Infectious Disease physicians, and Public Health Units*

- **Since May 2022, outbreaks of monkeypox cases have been reported among men who have sex with men (MSM) in multiple countries.**
- **Monkeypox is notifiable to NSW Health. Please look out for signs and symptoms consistent with monkeypox in patients at risk.**
- **If you suspect monkeypox immediately contact your local infectious diseases specialist.**
- **For up-to-date information, refer to the NSW Health website.**

- As of 5 August 2022, 27,562 confirmed cases of monkeypox have been reported globally in the current outbreak, predominantly among men who have sex with men (MSM).
- 34 cases have been notified in NSW. 32 cases were diagnosed in NSW, while 2 cases were diagnosed overseas and returned to NSW while infectious. All acquired their infection overseas except for 2 cases. A total of 57 cases of monkeypox have been reported in Australia.

**What are the symptoms of monkeypox?**

- Monkeypox is usually a self-limiting but unpleasant illness characterised by a rash. It may sometimes be severe and painful. A prodromal illness of fever, malaise, headache, myalgia, and lymphadenopathy may occur but many cases in this outbreak have presented with pimples or pustules first appearing in the genital area or buttocks.

**How is monkeypox transmitted in this international outbreak?**

- Skin to skin contact with a person infected with monkeypox (including sexual contact) has been the most important mode of transmission in this outbreak. Transmission by respiratory droplets in the prodromal phase and contact with clothing, linen or other contaminated items is also possible.

**How to manage a suspect monkeypox case**

- Please look out for signs and symptoms consistent with monkeypox, especially in sexually active MSM.
- Patients should remain isolated, and a telemedicine consultation arranged where possible. Those who present to an Emergency Department should be isolated and wear a surgical mask. Clinicians examining patients should wear appropriate PPE; please see the CEC IPC guidelines: https://www.health.nsw.gov.au/monkeypox-clinicians-info
- Contact the on-call Infectious Diseases/ Microbiology in your Local Health District for advice on clinical management and samples to collect.
- If monkeypox is suspected, collect samples per the PHLN guidelines and send these to the NSW Health Pathology-ICPMR laboratory at Westmead Hospital for monkeypox virus testing.
- Clinicians should ensure samples are expedited to ICPMR.
- Please call Infectious Diseases/ Microbiology at Westmead Hospital on 8890 5555 for advice, or if planning to admit the patient.
- Notify any suspected case to the public health unit for investigation, contact tracing and control measures.

**Vaccination**

- NSW Health has secured a limited supply of the JYNNEOS vaccine and will commence vaccination for high-risk groups from 8 August 2022.
- Vaccination will be initially targeted to those at greatest risk of severe illness and acquisition of the virus.

**Further information**

- Please contact your local Public Health Unit on 1300 066 055 to notify suspected cases.
- Australian Government monkeypox resources: https://www.health.gov.au/resources/collections/monkeypox-mpx-resources

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08 August 2022

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## APPENDIX C: Mpox factsheet for cases, 24 July 2022

NSW Health

Fact sheet

# Monkeypox: Information for cases

### Who is this factsheet for?

This factsheet is for people who have been diagnosed with monkeypox and who have been advised to self-isolate at home.

### What are the symptoms of monkeypox?

Most people with monkeypox have a mild illness and recover within a few weeks.

Monkeypox may begin with symptoms such as fever, headache, muscle aches, backache, pain around the anus/rectum, swollen lymph nodes, chills and exhaustion.

In some cases, it may begin with a rash, and some people with monkeypox may develop a rash without any other symptoms. The rash starts as flat, red lesions that develop into pustules which form crusts and fall off. A notable symptom of this outbreak is that the rash may first appear in the genital area, anus or buttocks.

### How does monkeypox spread?

Monkeypox mainly spreads through close skin-to-skin contact with someone who has monkeypox, such as when you are having sex, and by direct contact with infected bodily fluids, lesions, ulcers or scabs on the skin or in the mouth, or contact with contaminated objects, such as bedding, towels or clothes.

Less commonly, it can also spread from one person to another through prolonged close contact by inhaling respiratory droplets that carry the virus.

People with monkeypox are infectious from the time they first get any symptoms until all the lesions have crusted, scabs have fallen off and a fresh layer of skin has formed underneath.

It may be passed on during sex or close intimate contact. It is not known how long monkeypox virus remains present in semen and other genital excretions. People who have recovered from monkeypox should use condoms when engaging in sexual activity for eight weeks after recovery.

### How is monkeypox treated?

Most people with monkeypox only need regular over-the-counter pain medicines and oral fluids and can be monitored by their GP or treating clinician. A few patients may need supportive management such as intravenous fluids and medicine to control fever or pain.

There are antiviral medications available that may help to treat people with severe illness.

### What happens when I am diagnosed with monkeypox?

- Public health units, sexual health clinics, your GP or regular doctor, and infectious diseases physicians may all be involved in the management of your monkeypox infection.
- Your local public health unit will interview you to identify, assess and follow-up any contacts with whom you may have been in contact while infectious. The public health unit will follow-up all high-risk (e.g. sexual partners and household members) and medium-risk

(e.g. social or workplace) contacts to give them advice and monitor them for symptoms of monkeypox infection.

Your day-to-day health will be managed either by your regular GP or sexual health clinician, or by an infectious diseases physician from your local hospital.

## Who should I call if my symptoms get worse or I am concerned about my health?

If you are experiencing pain or discomfort, or you are concerned about any symptoms you may have, you should contact your GP, sexual health clinician, or the infectious diseases physician from your local hospital for immediate care. The doctor who is managing your day-to-day care will advise you who to call if you need help on weekends or out-of-hours.

- In an emergency call Triple Zero (000) immediately. Please tell doctors and other healthcare workers that you have been diagnosed with monkeypox. Wear a surgical mask if you go to a GP, hospital or ambulance.

## What is self-isolation? What do I need to do?

Isolation is an effective measure to reduce the spread of disease. Self-isolation means staying in your home or accommodation and remaining separated from others.

If you have monkeypox and you are self-isolating at home while infectious, you should:

- Isolate in a separate room, away from any other household members
- Avoid contact with any other household members
- Use a separate bathroom, if available. If you have to share a bathroom with others, it must be cleaned after each time you use it. For advice on cleaning and disinfecting your home while you are in self-isolation, please see the Clinical Excellence Commission Household Cleaning and Disinfection Information – Monkeypox
- Not go to work, school or public places (including shops, parks, beaches or gyms)
- Not have any visitors in your home
- Practise good hand and respiratory hygiene. Wear a surgical mask when in shared spaces and regularly wash your hands with soap and water or use an alcohol-based hand sanitiser
- Not leave your home except if you require follow-up medical care, or for solo outdoor exercise. If you need to leave your home, you should wear a surgical mask and cover any exposed lesions
- Ask friends or relatives to help with buying groceries and other essential items, including medication. They should leave these items outside your front door for you to collect
- Use designated household items (e.g. clothes, bed linen, towels, toothbrush, crockery and cutlery) and do not share these items with anyone else
- Ensure that your designated household items are not handled by others without personal protective equipment (surgical mask, gloves, gown)

- Not share food or drink with other people
- Clean high-touch surfaces such as door handles and light switches regularly with disinfectant. For advice on cleaning and disinfecting your home while you are in self-isolation, please see the Clinical Excellence Commission Household Cleaning and Disinfection Information – Monkeypox
- Abstain from sexual activity while infectious, and continue to use condoms for eight weeks after you have recovered
- Avoid contact with mammal pets including cats and dogs, and particularly avoid contact with any pet rodents (e.g. hamsters, gerbils, mice, rats, guinea pigs).

If you are unable to self-isolate at home you should:

- Discuss this with your local public health unit. You will need to arrange for appropriate accommodation for either yourself or your household contacts so you can isolate effectively to prevent infecting other people. The public health unit can provide support with this. This is particularly important if there are children or pregnant women in your household.

Please contact your local public health unit on **1300 066 055** if you require advice or support.

## When can I leave self-isolation?

If you are a **suspected case**, you should self-isolate until a negative laboratory test result is received.

If you are a **confirmed or probable case**, you should self-isolate until all lesions have crusted, scabs have fallen off and a fresh layer of skin has formed underneath.

The doctor who is managing your care and the local infectious diseases physicians will review your case and your symptoms and advise on when you can be released from isolation.

## What happens when my self-isolation has finished?

You must thoroughly clean and disinfect your home when you leave self-isolation. Special attention must be paid to items and surfaces that were in direct contact with your skin.

Monkeypox virus can survive on bed linen, towels, clothing and on environmental surfaces, including fabric surfaces such as sofas, cushions and beds. It is important to clean and disinfect any areas where you have spent time during your infectious period, including vehicles.

Advice on how to clean and disinfect your home at the end of your self-isolation period can be found in the Clinical Excellence Commission Household Cleaning and Disinfection Information – Monkeypox.

It is not known how long monkeypox virus remains present in semen and other genital excretions. You should use condoms when engaging in sexual activity for eight weeks after you recover from monkeypox. This is a precaution to reduce the risk of spreading infection to sexual partners.

When your self-isolation has finished you can return to work or school, and resume social activities.

## What support is available while I am in self-isolation?

Staying at home for a prolonged period can be difficult, frustrating and lonely. It is important to remember to take care of your mind as well as your body and to get support if you need it. Stay in touch with family and friends over the phone or on social media.

Help and support is available if you need it by calling:

NSW Mental Health Line – 1800 011 511

Beyond Blue helpline – 1800 512 348

Lifeline – 13 11 14

## Further information

Please refer to the NSW Health Monkeypox factsheet for further information. You can also call your local public health unit on **1300 066 055** or visit the NSW Health website www.health.nsw.gov.au

# Part B: Investigation of a foodborne illness outbreak in the Nepean Blue Mountains Local Health District, NSW, November 2022

In November 2022 the Nepean Blue Mountains public health unit (PHU) investigated a foodborne illness outbreak linked to a high tea event at a hotel in the Blue Mountains. I joined this investigation and conducted the analysis as a learning experience.

## Introduction

Foodborne illness in two or more related cases is notifiable in NSW under the *New South Wales Public Health Act 2010 No 127*. The public health priority is high, with PHUs to respond on the day of the notification. [1] Clusters of foodborne illness may be notified to PHUs by hospitals or medical practitioners, through routine surveillance of enteric disease or emergency department presentations, or by the New South Wales Food Authority (NSWFA) following a complaint by a member of the public through the NSWFA consumer complaints line.

When the NSWFA receives a consumer complaint of foodborne illness in two or more related cases and if the ill people do not reside in the same house, the NSWFA refers the complaint to the Enterics Unit who refers it to the public health unit for further investigation.

The NSWFA, the PHU, and Health Protection NSW work together closely on the investigations of suspected foodborne illness outbreaks. The PHU is responsible for the epidemiological investigation, which includes interviewing cases to count them and characterise their illness and exposures, facilitating medical tests and the collection of appropriate specimens from cases, and conducting epidemiological analyses to identify any potential links to food. The NSWFA is responsible for the environmental food investigation, which includes assessing the safety of food handling procedures, collecting and testing food and environmental samples, and tracing back food suppliers or manufacturers that may be linked to an outbreak. Health Protection NSW is responsible for the coordination of outbreak investigations that occur across more than one PHU.

The PHU and NSWFA are jointly responsible for determining whether there is an ongoing risk to the public from a foodborne illness outbreak stemming from a commercial food premises, and, if so, taking action to minimise or eliminate that risk, such removing suspected contaminated food from sale or supply, remediation of unsafe food handling procedures, or restricting a suspected infectious food handler from work or specific duties.

The Enterics Team at Health Protection NSW was notified by the NSWFA on 28 November 2022 of an alleged foodborne illness complaint regarding a cluster of gastroenteritis illness in a group of people who had all eaten a high tea meal at the hotel between 11am and 12:45pm on Saturday 26 November 2022. The complaint noted onset of vomiting, diarrhoea, and abdominal cramps early on Saturday 27 November, and reported 12 people unwell with similar symptoms. The complainant was a member of the group who had become ill.

The Enterics team notified the Nepean Blue Mountains (NBM) PHU of the complaint and the PHU commenced an investigation into the source of the foodborne illness outbreak. The PHU called the complainant to gather details of the meal, the illness, and the attendees.

The NBM Local Health District (LHD) is located on lands of the Darug, Gundungurra and Wiradjuri people, across the Penrith, Hawkesbury, Blue Mountains and Lithgow local government areas to the west and northwest of metropolitan Sydney. The LHD has a population of approximately 384,000 living in a mix of rural, remote, and concentrated suburban areas covering almost 9,179 $km^2$.

The aim of the investigation was to identify the extent and source of the outbreak in order to determine public health measures to take to prevent further risk to other patrons or staff of the venue.

However, as the investigation progressed and in the absence of an identified pathogen or reports of other groups of people affected, the investigating team prioritised this investigation as lower than other case investigations and public health activities and decided to conclude their investigation after the interviews were completed. We could not be sure that the cluster of illness was associated with the venue, or associated with other shared exposures before and after the event, or a viral gastroenteritis cause from one of the group members. Further steps, such as a traceback of constituent ingredients used in the food served and interviewing other patrons and staff of the venue who were present on the day were not conducted.

The control guidelines state that for suspected point source outbreaks, “where it can be established that the only event that links most cases is a common meal, then the exposure investigation can usually be limited to foods and other exposures that occurred associated with that meal.” [1]

I carried out the data analysis and compiled this report as a learning exercise in order to gain experience in foodborne illness investigations, analysis of cohort exposure and outcome data in an outbreak setting, and writing outbreak reports.

In this report, I describe the investigation and the epidemiological characteristics of the outbreak, and discuss the difficulties and limitations of a suspected foodborne illness outbreak investigation in the

absence of specimens or an identified pathogen. I also make recommendations for improvements of these investigations.

## Methods

### Epidemiological investigation

We conducted a retrospective cohort study on a large, discrete group of people who ate at the hotel and another who ate leftovers, to aid in the identification of the causative agent and determine the route of transmission of the causative agent. The primary complainant provided a list of 20 names, of whom 19 had attended the event and one had eaten leftover food brought home by an attendee. A full list of food items served at the meals and their ingredients was obtained from the venue.

The PHU developed a questionnaire in Excel and all interviewers inputted answers directly into the spreadsheet saved in the NBM PHU SharePoint and accessible to NBM PHU staff and me. Each of the seven interviewers was assigned between one and eight attendees to interview and the name of the interviewer was inserted in a column in the spreadsheet. The spreadsheet collected demographic information (age, sex, postcode), contact information (name, phone number, email address), symptom information (date and time of symptom onset, individual symptoms, date of resolution of illness, medical attention sought), any illnesses prior to the event, any samples taken, group interactions (other events attended jointly, household contacts within the cohort), food exposures (all individual items), and free text additional comments. Staff in NBM PHU and I conducted the interviews by telephone over two days, four days after the function was held. Exposure information was collected for both food exposures and person-to -person transmission.

### Case definition

We defined a case as any person who was previously well, but after consuming food from the venue on 26 November (either at the venue or leftover food from the venue), became ill with diarrhoea or vomiting within 48 hours of consumption.

### Statistical analysis

We calculated attack rates in the exposed and unexposed groups for each individual food item and risk ratios with 95% confidence intervals and p values using Fisher's exact tests.

Statistical analysis was carried out using Stata version 16. Given the overlap in ingredients for the Caesar sandwich and the egg sandwich, I created an exposure of 'Any egg-filled sandwich.' The egg sandwich and the Caesar sandwich had the same filling of boiled eggs, Caesar dressing, and store-bought mayonnaise, with the Caesar sandwich including anchovies and crispy bacon in addition.

### Environmental investigation

In NSW, environmental investigations are conducted by NSWFA or the relevant local Council. The NSWFA contacted the local Council to see if there were any known issues relating to the venue. The Council conducted an inspection of the venue.

An unrelated and much larger foodborne illness outbreak with an identified pathogen had been notified five days after this one, and the resources of NSWFA were deployed to the extensive environmental investigation of the later outbreak.

### Microbiological investigation

No samples were submitted for microbiological investigation. All cases were asked if they sought medical attention and if they had any specimens collected. None did. If any cases report at interview that their symptoms are continuing, they are requested to visit a doctor and have a specimen taken for microbiological testing. All cases in this outbreak reported at interview that their symptoms had resolved.

## Results

In total 19 people attended the high tea event at the hotel. All were female. There were 17 adults and two children. The children were aged 8 months and 3 years. One male did not attend the event but lives with a person who did attend and ate leftover food that was brought home from the event.

### Response rate

Of the 20 people identified who had consumed food from the venue, the PHU conducted 16 interviews to gather demographic, clinical, and, using the menu list, exposure information. One person provided information for herself and on behalf of her two children, who had both attended the event. Two attendees of the event were unable to be contacted for interview.

The cohort was composed of 17 females and one male, median age 25 (range 8 months to 76 years). Most people in the cohort lived in the South Western Sydney local health district. A summary of cohort is contained in Table 1.

There were 12 people meeting the case definition, and six people who did not become ill after eating the food. None of the sick people sought medical attention for their gastrointestinal symptoms and no stool specimens were collected.

## Summary of the cases

Of the cases, 11 cases were adults, and one case was a 3-year-old child. 92% of cases were female. The median age was 25.

**Table 1: Summary of the cohort (n=18)**

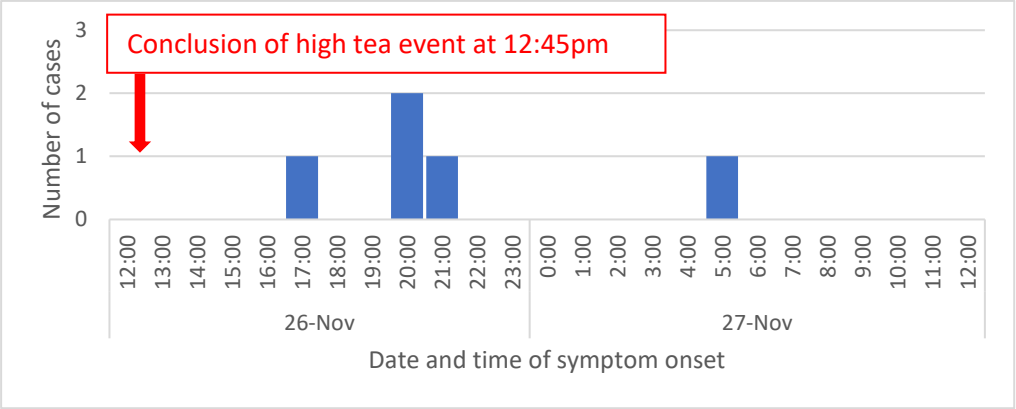
| | Sick | Not sick | Total |
|---|---|---|---|
| | n=12 | n=6 | n=18 |
| Sex n (%) | | | |
| Male | 1 (8) | 0 (0) | 1 (6) |
| Female | 11 (92) | 6 (100) | 17 (94) |
| Median age in years (IQR) | 25 (22-44) | 26 (22-59) | 25 (22-52) |
| Local Health District of residence n (%) | | | |
| South Western Sydney | 7 (58) | 1 (17) | 8 (44) |
| Southern NSW | 2 (17) | 0 (0) | 2 (11) |
| Hunter New England | 1 (8) | 2 (33) | 3 (17) |
| Nepean Blue Mountains | 1 (8) | 1 (17) | 2 (11) |
| South Eastern Sydney | 1 (8) | 1 (17) | 2 (11) |
| Illawarra Shoalhaven | 0 (0) | 1 (17) | 1 (6) |

## Symptom profile

Symptom onsets ranged between 5pm on 26 November and 27 November 2022. A time of symptom onset was only recorded during interview for five of the cases (Figure 1). The remaining seven ill cases only had a date of onset recorded, likely due to the absence of a separate question and data collection column for time of onset. The questionnaire in the data collection spreadsheet combined date and time of symptom onset into one cell and one data entry column. There was no validation on the cells to ensure that both date and time were recorded. As a result, time of onset was missing for seven cases, which has limited our ability to analyse symptom onset time and duration of illness in detail.

Six people reported symptom onset on 26 November and one person, who did not attend the event but consumed leftover food brought home by an attendee, reported a symptom onset of 27 November. The time of consumption of the leftovers was not recorded for this case.

Figure 1: Epi curve of symptom onset, 26–27 November 2022, cases with known onset time (n=5)




All 12 cases reported diarrhoea, which was accompanied by abdominal pain for 11 of the 12 cases. None of the cases reported bloody diarrhoea. While five cases reported nausea, only one case reported vomiting (Table 2).

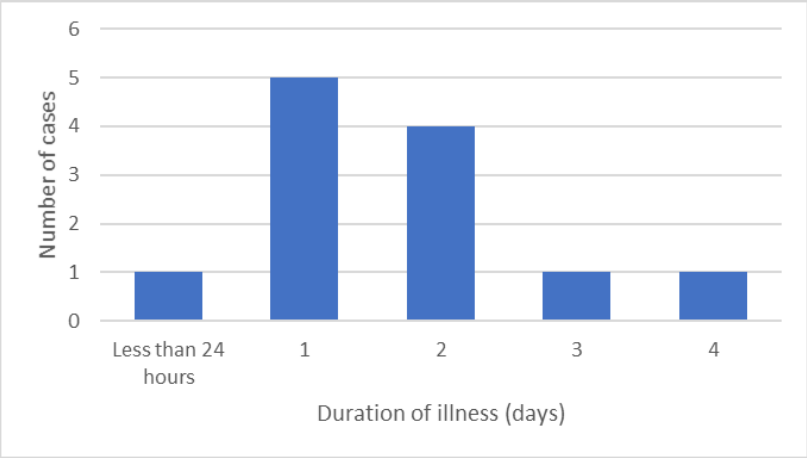
Table 2: Table of symptoms experienced by cases and their frequency, 26-30 November 2022

| Symptom | Number of cases experiencing this symptom (%) |
|---|---|
| Diarrhoea | 12 (100) |
| Bloody diarrhoea | 0 (0) |
| Abdominal pain/cramps | 11 (91.7) |
| Nausea | 5 (41.7) |
| Headache | 1 (8.3) |
| Vomiting | 1 (8.3) |
| Fever | 1 (8.3) |
| Arthralgia | 0 (0) |

All cases had a date of symptom onset and a date of illness resolution recorded. All cases reported at interview that their symptoms had resolved. Duration of illness is only able to be calculated in days for the majority of cases, with the exception of the five cases with a time of symptom onset recorded, where a more detailed length of illness could be calculated. The duration of illness ranged from less than 24 hours to four days, with median duration of 1.5 days.

In the absence of any patient specimens no pathogen was identified.

Figure 2: Duration of illness for cases (n=12)




## Exposure information

The function was a bridal shower high tea attended by a group of women with a mix of family groups (mothers, daughters, sisters) and friends. We do not know whether attendees sat at one table or multiple tables, or whether cases sat clustered together at the table(s) as this did not form part of the questionnaire.

None of the people interviewed reported having any household members ill or any contact with ill people prior to the event.

The group shared other exposures together on the day of the high tea event, which complicated efforts to determine a clear exposure of concern. Fifteen attendees (nine cases) travelled together to the event, in five cars. Eight of the high tea attendees (four cases) attended a second event, a 'Paint and Sip' group painting activity together after the high tea, where crackers and strawberries were consumed.

Attack rates and risk ratios were calculated for all food exposures at the high tea venue (Table 3). Only three individual items exhibited any significance (RR >1, 95% CI did not cross 1, p-value on Fishers exact test <0.05). These were the cucumber and tomato sandwich, the egg sandwich and the curry chicken tartlet, all with eight people exposed, a 100% attack rate in exposed people, and a risk ratio of 2.50 (95% CI 1.17-5.34) (Table 3).

The sausage roll had a risk ratio of 5.50 and p-value on Fishers exact test of 0.004. This is the highest risk ratio for an individual item and the lowest p-value of any of the tests, however, the confidence intervals for this item crossed 1 (95% CI 0.91-33.18).

The combined exposure of 'Any egg-filled sandwich' gave a strong signal of significance as an implicated food exposure, with a 100% attack rate in 11 people exposed and a risk ratio of 7.0 (95% CI 1.14-42.97).

Stratified analysis did not provide more information as there was significant overlap in food consumption between cases. Examining the three individual implicated items by removing one of the other items from the analysis increased the risk ratios from 2.5 to 4, but these results were less statistically significant possibly due to the low numbers involved.

Attendees reported that the sandwiches were all served on platters together and so cross-contamination between the sandwiches cannot be ruled out.

Table 3: Analysis of food exposures with risk ratios

| | Exposed | | | | Not exposed | | | | | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sick | Not sick | Total | Attack rate | Sick | Not sick | Total | Attack rate | RR | 95% CI | | Fishers exact |
| Plain scone | 9 | 4 | 13 | 0.69 | 3 | 2 | 5 | 0.60 | 1.15 | 0.52 | 2.57 | 0.56 |
| Fruit scone | 5 | 2 | 7 | 0.71 | 7 | 4 | 11 | 0.64 | 1.12 | 0.59 | 2.14 | 0.57 |
| Strawberry jam | 10 | 5 | 15 | 0.67 | 2 | 1 | 3 | 0.67 | 1 | 0.42 | 2.40 | 0.73 |
| Cream | 10 | 4 | 14 | 0.71 | 2 | 2 | 4 | 0.50 | 1.43 | 0.51 | 4.02 | 0.41 |
| Champagne | 4 | 3 | 7 | 0.57 | 8 | 3 | 11 | 0.73 | 0.79 | 0.38 | 1.64 | 0.43 |
| Tea or coffee | 10 | 3 | 13 | 0.77 | 2 | 3 | 5 | 0.40 | 1.92 | 0.63 | 5.86 | 0.18 |
| Berry gateau | 4 | 1 | 5 | 0.80 | 8 | 5 | 13 | 0.62 | 1.30 | 0.70 | 2.40 | 0.44 |
| Caramel and chocolate tart | 5 | 1 | 6 | 0.83 | 7 | 5 | 12 | 0.58 | 1.43 | 0.79 | 2.60 | 0.31 |
| Tropical verrine | 8 | 3 | 11 | 0.73 | 4 | 3 | 7 | 0.57 | 1.27 | 0.61 | 2.66 | 0.43 |
| Pistachio cupcake | 5 | 1 | 6 | 0.83 | 7 | 5 | 12 | 0.58 | 1.43 | 0.79 | 2.60 | 0.31 |
| Raspberry macaron | 8 | 2 | 10 | 0.80 | 4 | 4 | 8 | 0.50 | 1.60 | 0.75 | 3.42 | 0.20 |
| Roasted lamb wrap | 9 | 1 | 10 | 0.90 | 3 | 5 | 8 | 0.38 | 2.40 | 0.96 | 6.01 | 0.03 |
| Caesar sandwich | 4 | 0 | 4 | 1.00 | 8 | 6 | 14 | 0.57 | 1.75 | 1.11 | 2.75 | 0.16 |
| Cucumber tomato sandwich | 8 | 0 | 8 | 1.00 | 4 | 6 | 10 | 0.40 | 2.50 | 1.17 | 5.34 | 0.01 |
| Smoked salmon brioche | 6 | 1 | 7 | 0.86 | 6 | 5 | 11 | 0.55 | 1.57 | 0.85 | 2.92 | 0.20 |
| Sausage roll | 11 | 1 | 12 | 0.92 | 1 | 5 | 6 | 0.17 | 5.50 | 0.91 | 33.18 | 0.004 |
| Curry chicken tartlet | 8 | 0 | 8 | 1.00 | 4 | 6 | 10 | 0.40 | 2.50 | 1.17 | 5.34 | 0.01 |
| Vegetarian wrap | 1 | 1 | 2 | 0.50 | 11 | 5 | 16 | 0.69 | 0.73 | 0.17 | 3.02 | 0.57 |
| Vegetarian spring rolls | 1 | 1 | 2 | 0.50 | 11 | 5 | 16 | 0.69 | 0.73 | 0.17 | 3.02 | 0.57 |
| Avocado cucumber rice paper rolls | 1 | 2 | 3 | 0.33 | 11 | 4 | 15 | 0.73 | 0.45 | 0.09 | 2.32 | 0.25 |
| Egg sandwich | 8 | 0 | 8 | 1.00 | 4 | 6 | 10 | 0.40 | 2.50 | 1.17 | 5.34 | 0.01 |
| Combined variable: ANY EGG FILLED SANDWICH | 11 | 0 | 11 | 1.00 | 1 | 6 | 7 | 0.14 | 7.00 | 1.14 | 42.97 | 0.0004 |

### Environmental inspection

The NSWFA contacted the local Council to see if there were any known issues relating to the venue. The Council last inspected the premises in June 2022 and found all kitchens were satisfactory and maintained to a high standard. No complaints about the venue had been received by the Council. No further complaints about the venue had been received by either the NSWFA, the PHU or the venue.

The local council did conduct an inspection of the venue several weeks after the event and found all kitchens satisfactory.

### Control measures

The complaint and subsequent investigation did trigger an inspection of the venue by the local council. No further control measures were undertaken due to the absence of an identified pathogen or a definitive link to the venue.

## Discussion

### Causative agent

Despite the absence of a confirmed pathogen from microbiological investigation, we are able to consider potential causative agents using information about the timing and nature of the symptoms and the foods consumed by the group.

A short incubation period can suggest a toxin or a viral pathogen, such as norovirus, however, cases with viral gastroenteritis usually report high rates of vomiting and nausea, which were not seen in our cohort. Parasitic pathogens usually have longer incubation periods (median 7 days), and the high tea meal did not include any obvious ingredients likely to have caused gastroenteritis due to a non-microbial toxin or chemical consumption. The predominance of diarrhoea and abdominal pain experienced by our cohort, together with the relative absence of vomiting, suggests a bacterial pathogen is more likely.

Based on the symptom profiles and incubation times outlined in the CDC's *Guide to Confirming an Etiology in Foodborne Disease Outbreak*, the most likely pathogen is either *Clostridium perfringens*, a nontyphoidal *Salmonella*, or Enterotoxigenic *Escherichia coli* (ETEC). [2] *Clostridium perfringens* is characterised by a short incubation period of 6-24 hours, and symptoms of diarrhoea and abdominal cramps, with vomiting and fever uncommon. ETEC has a similarly short incubation period of 6-48 hours, and also causes symptoms of diarrhoea, abdominal cramps, and nausea, with vomiting and fever less common. Nontyphoidal *Salmonella* species cause diarrhoea, often with fever and abdominal cramps, and have an incubation period of 6-48 hours, although some serovars can have a longer incubation period of up to 10 days.

The short incubation period (less than 12 hours between consumption of the high tea meal and symptom onset for 10 of the 12 cases) excludes *Campylobacter* species, which has an incubation time of 2-10 days and

often causes bloody diarrhoea, which none of our cohort reported. Enterohemorrhagic *Escherichia coli* (such as Shiga-like toxin-producing *E. coli*, or STEC) and *Shigella* species bacteria are also more likely to cause bloody diarrhoea in cases.

### Vehicle for transmission

The egg filling is biologically plausible as the cause of the bacterial gastroenteritis as egg, mayonnaise and egg-based dressings such as Caesar dressing are high-risk food items for bacterial growth due to their origin, preparation and storage. Egg sandwiches have previously been implicated as a vehicle for transmission in foodborne illness outbreaks in England, Wales and China. [3-5] In all of these outbreaks the pathogen responsible for the gastroenteritis outbreak was *Salmonella spp*. The strength of association for the combined exposure of any egg-filled sandwich indicates it could be source of the illness.

The sausage roll was also as a suspect item following the univariate analysis, and could be a plausible vehicle for transmission if it had not been cooked at sufficiently high temperatures or for a sufficient length of time.

With a viral gastroenteritis pathogen such as norovirus we would expect to see ongoing transmission within households. The only case who did not attend the event ate the leftover food from the venue. None of the attendees reported any illness in their household before or after the event.

### Limitations

This investigation was limited by many factors. The absence of any specimens from any of the cases made definitive identification of a pathogen impossible. This, in turn, has limited the scope of the subsequent investigations, as we had limited evidence to proceed with environmental investigations or conduct active case finding by attempting to obtain lists of other diners at the venue for interview. Without microbiological evidence or evidence of an ongoing or more extensive outbreak the investigation was curtailed.

A menu with list of the constituent ingredients was supplied by the venue, which was used in the food exposure questionnaire and to consider potential vehicles for transmission, however, in the absence of an identified pathogen or evidence of ongoing risk to the community, no environmental sampling or traceback of ingredients was conducted by the NSWFA. An investigation into the premises and a review of food handling practices by the NSWFA may have uncovered evidence to inform the investigation.

The NSWFA and local councils have limited resources for investigations and these resources need to be prioritised. In 2022, 35 potential foodborne illness outbreaks were notified to the Enterics Unit. Eight investigations took place in December 2022 alone, absorbing considerable resources in Health Protection NSW, NSWFA and the PHUs. Without evidence of ongoing risk to the public this investigation was not a priority.

The epidemiological investigation was hampered by poor data quality in some areas. The questionnaire in the data collection spreadsheet combined date and time of symptom onset into one cell and one data entry column. There was no validation on the cells to ensure that both date and time were recorded. As a result,

time of symptom onset was not collected for all cases, which limited my ability to analyse the time from the event to the onset of illness and the duration of illness for the cases.

The manager of the venue did not report any other complaints of illness from patrons on that day or in the days preceding the event. We did not obtain lists of other attendees at the venue that day and did not contact any staff of the venue to inquire if they had been ill.

The cohort was small and subsequently the statistical analysis has been limited by small numbers. If resources had permitted it, the investigation would have been improved by active case finding with other patrons who dined on the same day and staff at the venue.

### Recommendations

We recommend the use of standardised questionnaires to systematically collect key data, using clear and separate questions, such as collecting the time of symptom onset separate to the date of symptom onset. This will assist interviewers to explicitly collect both pieces of information. Collecting both date and time of symptom onset is essential for analysis of the time in hours between exposure and illness. This information contributes to our investigation into and understanding of the epidemiology of foodborne illness.

## Conclusion

These kind of foodborne illness investigations are challenging as there is no clear single exposure to which the illness can be attributed and no samples available for testing. With limited resources and no evidence of ongoing public health risk, these events are not prioritised for further investigation. However, the investigation and analysis were useful learning experiences as they allowed me to apply the steps of an outbreak investigation, conduct the analysis, and become familiar with the method and procedures for responding to foodborne illness outbreak notifications in NSW.

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# CHAPTER 4

## Evaluate a surveillance system or other health information system

Evaluation of the NSW multidrug resistant organism surveillance system

## Chapter 4: Table of contents

## List of abbreviations

| | |
|---|---|
| ACSQHC | Australian Commission on Safety and Quality in Health Care |
| AMR | Antimicrobial resistance |
| AURA | Antimicrobial Use and Resistance in Australia Surveillance System |
| CARAlert | National Alert System for Critical Antimicrobial Resistances |
| CDC | US Centers for Disease Control and Prevention |
| CEC | Clinical Excellence Commission |
| CPE | Carbapenemase-producing *Enterobacterales* |
| | Carbapenemase-producing *Enterobacteriaceae* |
| CRE | Carbapenem-resistant *Enterobacteriaceae* |
| CRPA | Carbapenem-resistant *Pseudomonas aeruginosa* |
| ECDC | European Centre for Disease Prevention and Control |
| ELR | Electronic laboratory record |
| HAI | Healthcare associated infection |
| HPNSW | Health Protection New South Wales |
| ICPMR | Institute of Clinical Pathology and Medical Research, Westmead |
| IHACPA | Independent Health and Aged Care Pricing Authority |
| IMP | Imipenemase |
| IPC | Infection prevention and control |
| KPC | *Klebsiella pneumoniae* carbapenemase |
| MDR | Multidrug resistant |
| MRAB | Multidrug-resistant *Acinetobacter baumannii* |
| MRO | Multidrug resistant organism |
| MSRA | Methicillin-resistant *Staphylococcus aureus* |
| NCIMS | Notifiable Conditions Information Management System |
| NDM | New-Delhi-metallo-β-lactamase |
| OXA | Oxacillinase |
| VIM | Verona integron–encoded metallo-β-lactamase |
| VRE | Vancomycin-resistant *Enterococci* |
| WGS | Whole genome sequencing |

## Preface

This chapter presents an evaluation of the New South Wales (NSW) multidrug resistant organism (MRO) surveillance system. This chapter addresses the following competency:

- Establish or evaluate a surveillance system or other health information system

## My role

I received the outline of a proposed evaluation and a background briefing in April 2021 and began working on this project in late May 2021. I was diverted to the Sydney COVID-19 outbreak response full time in June and returned to the evaluation in October 2021.

I took the lead role in this project, supervised by Dr Hendrik Camphor and Dr Katherine Todd. From the outline that Katherine gave me, I developed the objectives, the evaluation plan and the methods. Using the CDC framework for evaluating surveillance systems, I developed questions to evaluate each attribute. I conducted semi-structured interviews with key informants between October and December 2021, via online meeting platforms due to the ongoing lockdown and travel constraints. I also participated in an MRO Summit organised by the CEC in October 2022 with infection prevention and control (IPC) teams from across New South Wales (NSW) to look at MRO surveillance.

## Key reflections

Through this project I gained technical antimicrobial resistance (AMR) knowledge about organisms, resistance genes, plasmids, typing, and how to read and interpret genomic data for drug resistant organisms. I also learned about the challenges of incorporating sequencing data into communicable disease surveillance systems, both in terms of technical data management systems and analysis, but also the interpretation of the data for different audiences with varying levels of experience and different data uses. The additional value of genomics in the field of AMR is enormous.

Methodically mapping the entire process of the system was a useful experience to understand the many points at which the system can fail, from the decision to collect (or not!) a sample, to the timely processing of samples in a constrained lab setting, right through to analyses to link genomic clusters and disseminate that information back to people who can act upon it. I enjoyed further developing my qualitative research skills by conducting and analysing the interviews.

## Public health implications

This project contributed to a larger, and first ever, evaluation of NSW's MRO surveillance system, and was an important checkpoint in the evolution of the system, particularly in the context of increasing national interest in MRO and AMR surveillance. My evaluation showed several areas for improvement, and recommendations for improving the system, contained at the end of this chapter, have been

provided to the Executive Director of Health Protection NSW and other delegates for consideration and further action.

## Acknowledgements

Thank you to Katherine Todd for delivering this project to me and for being an enthusiastic and supportive guide throughout, despite changing roles many times, and to Hendrik Camphor for his dedicated guardianship of the system during his tenure as MRO Epidemiologist. Thank you to Jenn Case and Keira Glasgow for all their input into this project from conception to conclusion. Big thanks to Grace Blackwell for arriving at NSW Health at a crucial moment and bringing her enthusiasm and expertise to MRO surveillance, and for our excellent MRO/AMR chats that always helped me feel like I was on the right track. Finally, I am enormously grateful to Keren Francis for her moral support, her practical assistance with this evaluation, and for sharing her time and her expertise so generously with me.

## Ethics

Ethics approval was granted by the Australian National University Human Research Ethics Committee under protocol 2017/909.

## Abstract

### Introduction

Multidrug resistant organisms (MROs) are microorganisms that are resistant to one or more classes of antimicrobials. Infections involving MROs result in prolonged and more frequent hospital admissions; longer, more expensive and more toxic treatments; and increased morbidity and mortality. Work began in the New South Wales (NSW) Ministry of Health in 2017 to determine a list of priority organisms for surveillance, develop a network across NSW to advance surveillance and control of MROs, and implement state-wide public health surveillance of MROs. In February 2019 carbapenemase-producing *Enterobacterales* (CPE) infection and colonisation was made a laboratory notifiable condition in NSW and the MRO surveillance system was established. In June 2020 *Candida auris* infection and colonisation was also added to the list of laboratory notifiable conditions in NSW.

### Methods

Using the CDC's *Updated Guidelines for Evaluating Public Health Surveillance Systems* as a framework, this evaluation sought to describe the operation of the NSW MRO surveillance system, review its performance against its stated objectives, assess its performance according to a set of key attributes, and make recommendations for improvement. The evaluation methods included a review of the surveillance data from 2019–2023, and semi-structured interviews with key informants.

### Results

Eight semi-structured interviews were conducted with key informants. The first case of CPE was notified 5 March 2019. From its inception to 30 June 2023, the surveillance system has detected 1,683 CPE events and two *Candida auris* events. The majority of CPE cases were identified in acute health care services, however, cases have also been detected in community settings. The most identified organism in CPE is *Enterobacter hormaechei*. The most common resistance gene identified in NSW notifications is $bla_{\text{IMP-4}}$, which confers the ability to produce imipenemase. Beyond basic demographic and specimen details, the system does not collect any information about hospitalisation history or movements between facilities or wards, co-morbidities, current hospitalisation or treatment history such as the presence of indwelling devices or recent invasive procedures, or any travel history. The system is limited in its ability to describe the epidemiology of CPE in NSW or estimate its magnitude or scope, and beyond identifying clusters using genomics, the system does not routinely have any public health actions arising from its data collection.

## Conclusion

The surveillance system is moderately useful as a source of information about the prevalence of CPE in NSW, although the data it produces are not representative and the sensitivity of the system is poor. The system is further weakened by its partial duplication of other MRO surveillance systems that measure HAIs, and lack of integration into electronic lab notification and routine surveillance systems used in NSW. The system is manual, additionally complex, and lacks stability or universal acceptability. The data it produces are not returned to the system users in a timely fashion. Without enhanced surveillance data, the system has limited ability to identify transmission or inform strategies to control MROs in NSW.

## Introduction

Antimicrobials are drugs used to prevent and treat infections caused by bacteria, viruses, parasites, and fungi.[1] When these microorganisms no longer respond to antimicrobials this is described as antimicrobial resistance (AMR).[2] AMR is one of the greatest health threats facing the world in the twenty-first century.[1, 3-5] In 2013 England's Chief Medical Officer, Professor Dame Sally Davies, labelled AMR a "catastrophic threat" requiring global action[6], and in 2016 the United Nations General Assembly took up the issue of AMR, with the Director-General of the World Health Organization (WHO), Dr Margaret Chan, declaring that "antimicrobial resistance poses a fundamental threat to human health, development, and security… We are running out of time."[7] When antimicrobials become ineffective due to AMR, the resulting infections are harder to treat, and in some cases, may be impossible to treat.[4, 8] A systematic analysis estimated 4.95 million deaths globally in 2019 were associated with bacterial AMR,[3] and a US study finding that additional treatment costs of six key AMR threats in the USA in 2017 cost an estimated 4.6 billion USD.[9] Multidrug resistant organisms (MROs) are microorganisms that are resistant to one or more classes of antimicrobials. Infections involving MROs result in prolonged and more frequent hospital admissions; longer, more expensive and more toxic treatments; and increased morbidity and mortality.[8-10]

### Carbapenemase-producing *Enterobacteriaceae*

Carbapenemase-producing *Enterobacteriaceae* (CPE), also known as carbapenemase-producing *Enterobacterales*, are a serious emerging threat in AMR in Australia and internationally.[8, 10-20] Carbapenemases are enzymes capable of hydrolysing β-lactams, antibiotics such as penicillins, cephalosporins, monobactams, and carbapenems that are used to treat a broad range of bacterial infections, rendering them ineffective against the bacteria.[21] *Enterobacteriaceae* are a large family of Gram-negative enteric bacteria that commonly cause infections, especially in health care settings but also in community settings, such as *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp.[8, 20] By acquiring the ability to produce carbapenemases these bacteria become multidrug resistant organisms (MROs).

There are three classes of carbapenemases present among CPE.[8, 14, 21-24] Class A contains the *Klebsiella pneumoniae* carbapenemase (KPC) family, a high-burden carbapenemase with extensive global distribution.[8, 23] Class B contains the metallo-β-lactamases, such as the New-Delhi-metallo-β-lactamases (NDM), widespread in India, Pakistan, and Bangladesh,[8, 25, 26] the imipenemase (IMP) family, prevalent in Australia,[27, 28] and the Verona integron–encoded metallo-β-lactamase (VIM) family, with widespread global distribution.[24] Class D contains the oxacillinase (OXA) family, including OXA-23, OXA-24 and OXA-58 groups found mainly in *Acinetobacter baumannii* bacteria and causing substantial morbidity and mortality, particularly among ICU patients,[29, 30] and the OXA-48 group reported

predominantly in *Klebsiella pneumoniae*, endemic in Turkey and other Middle Eastern and North African countries but increasingly common worldwide, including in Australian outbreaks, and often difficult to detect without molecular methods.[8, 21, 23, 31, 32] All five of these carbapenemase families (KPC, NDM, IMP, VIM, OXA) have been identified in samples in New South Wales (NSW).

The spread of carbapenemase production in *Enterobacteriaceae* is driven by two mechanisms, clonal expansion and horizontal gene transfer via mobile genetic elements such as plasmids.[8, 13, 33] Advances in AMR research using genomics have expanded our understanding of carbapenem resistance genes, known as bla genes, which bestow upon bacteria the ability to produce carbapenemases, and allowed detailed examination of horizontal gene transfer via plasmids, a key mechanism by which resistance genes disseminate among different bacterial populations.[8, 21, 34] Plasmid-mediated horizontal gene transfer facilitates greater spread of carbapenemase production capacity between diverse bacteria species.[16, 20, 23, 33, 35] The extent to which either mechanism is responsible for the proliferation of carbapenemase production is a key epidemiological question to be answered by enhanced CPE surveillance, for which genomic analysis is essential.[8]

Identified risk factors for CPE acquisition include prior exposure to antibiotics not limited to carbapenems, previous long-term care or extended-stay hospitalisations, chronic co-morbidities, and invasive procedures such as surgery or endotracheal intubation, or presence of indwelling devices such as catheters, arterial lines, feeding tubes, or drains.[8, 12, 36-39] An additional risk factor for CPE acquisition is travel to endemic areas, particularly with healthcare exposures, either due to hospitalisation following illness or injury or medical tourism.[40-42] Mean duration of CPE carriage among hospitalised patients has been estimated at 86 days (95% credible interval 60–122 days).[43] Asymptomatic carriage, or colonisation, typically precedes CPE infections, and asymptomatic carriers can be a source of CPE transmission events in healthcare settings.[43]

### Surveillance of antimicrobial resistance

A global review of AMR surveillance conducted by the WHO in 2014 demonstrated that, despite the critical threat posed by AMR, major gaps in surveillance were apparent.[2] In particular, the review noted no consensus on or standardisation of AMR surveillance methodology and data collection, and surveillance based overwhelmingly on samples from seriously unwell patients in health care settings, with serious underrepresentation of community-acquired cases.[2]

The Australian Commission on Safety and Quality in Health Care (ACSQHC) established a national AMR surveillance system, the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System, in 2014, with funding from the Commonwealth Department of Health.[44] Since 2016 AURA has consolidated existing jurisdictional and national AMR surveillance datasets to produce a more

comprehensive and national picture of AMR in Australia. AURA operates the National Alert System for Critical Antimicrobial Resistances (CARAlert) to provide information on priority organisms that are resistant to last-line antimicrobials. Laboratories send notifications of MROs to CARAlert, where they are collated and distributed via jurisdictional mailing lists. Participation in CARAlert is voluntary and not all laboratories send their notifications to CARAlert. In 2021 management of AURA transferred from the ACSQHC to the Australian Government Department of Health and Aged Care.[45]

In NSW, the Clinical Excellence Commission (CEC) is responsible for surveillance of healthcare associated infections in NSW public health organisations that provide acute care services, as well as policy and strategy for antimicrobial stewardship and monitoring of antimicrobial usage in NSW. CPE is currently notifiable in five Australian jurisdictions: New South Wales, Victoria, South Australia, Western Australia, and Tasmania. It is under consideration to be made notifiable in the Australian Capital Territory.

### Establishment of the multidrug resistant organism (MRO) surveillance system in NSW

Following an outbreak of carbapenem-resistant *Klebsiella pneumoniae*, a type of CPE, in Victoria in 2012–2014,[46-48] the Communicable Diseases Network Australia established a working group to consider the public health implications of MROs at national level. In September 2017 their discussion paper, *Towards a nationally consistent public health response to multi-drug resistant organisms*, highlighted gaps in MRO surveillance as a key threat to MRO detection and control in Australia. [49]

In response, in January 2018 the CEC and Health Protection NSW (HPNSW) established the NSW MRO Surveillance and Response Reference Group to advise on key problematic MROs, determine a list of priority organisms for surveillance, and develop a network across NSW to advance surveillance and control of MROs. The network would then be used to develop guidelines and agreed emergency responses, standardise practices across facilities, and establish channels of communication.

Following a consultation process, in 2018 the MRO surveillance and response reference group identified five key MROs for surveillance in NSW:

- Carbapenem-resistant *Enterobacteriaceae* (CRE) / Carbapenemase-producing *Enterobacteriaceae* (CPE),
- Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA),
- Vancomycin-resistant *Enterococcus* (VRE),
- Methicillin-resistant *Staphylococcus aureus* (MRSA), and
- Multidrug-resistant *Acinetobacter baumannii* (MRAB).

Multidrug-resistant (MDR) *Candida auris* was added to the list of priority organisms in 2020.

Discussion at reference group and executive level centred on the best way to implement surveillance for the priority organisms, with consideration for the costs and benefits of making them laboratory notifiable conditions under the *Public Health Act.* The decision was made to begin with CPE surveillance, given that CPE events were thought to be uncommon, with CPE possibly not yet endemic, and therefore most amenable to public health control actions. It was hoped that a surveillance system with capability to find all CPE cases, investigate them and trace the origin and any contacts might contain the spread of CPE within NSW. Other jurisdictions, most notably Victoria,[46] were implementing systems for surveillance and control of CPE which showed significant promise. Expansion of the surveillance system to incorporate other priority organisms was planned to follow once CPE surveillance had been established and demonstrated to be useful.

The objective of the surveillance system in NSW was to monitor the epidemiology of CPE to inform prevention strategies and support control strategies. Little was known about the prevalence or endemicity of CPE in NSW, the distribution of resistance genes and any patterns of drug resistance. In February 2019 carbapenemase-producing *Enterobacterales* (CPE) infection and colonisation was made a laboratory notifiable condition in NSW under the *Public Health Act 2010, No 127* [50] and the MRO surveillance system was established to record and analyse CPE notifications.

**Case definitions: Carbapenemase-producing *Enterobacterales* (CPE)[51]**

Confirmed CPE Case: A person with a species of *Enterobacterales* isolated from clinical or screening specimens (infection or colonisation) where a carbapenemase gene is detected in a sample or isolate irrespective of phenotypic susceptibility.

Suspected CPE Case: A person with a species of *Enterobacterales* isolated from clinical or screening specimens (infection or colonisation), with phenotypic characteristics suggestive of carbapenemase gene presence but not yet confirmed.

*Note: Only molecular test results for confirmed cases are to be notified*

In June 2020 *Candida auris* infection and colonisation was added to the list of laboratory notifiable conditions in NSW. MDR *Candida auris* is of particular concern due to its recognition internationally as a healthcare-acquired infection with potential for epidemic spread. [52]

MDR *C. auris* is a yeast that causes invasive infections and is resistant to the first-line antifungal, fluconazole, with variable susceptibility to other antifungals. [53] It has been identified as a serious threat by the US Centers for Disease Control and Prevention (CDC) [54], the European Centre for Disease

Prevention and Control (ECDC) [55], and Public Health England [56] due to its capacity for persistent and hard-to-control outbreaks in healthcare settings. [57]

The first notifications of *C. auris* in NSW arrived in early 2022, after the reopening of international borders. CARAlert, the voluntary national surveillance system, did record two notifications in NSW in 2019 and two notifications in 2020, prior to it becoming notifiable in NSW. Cases of *C. auris* reported in Australia have typically been in admitted patients who have spent time as patients in healthcare facilities abroad. [58, 59] Figure 1 shows a timeline of key events in the NSW MRO surveillance system.

## Objectives of the evaluation

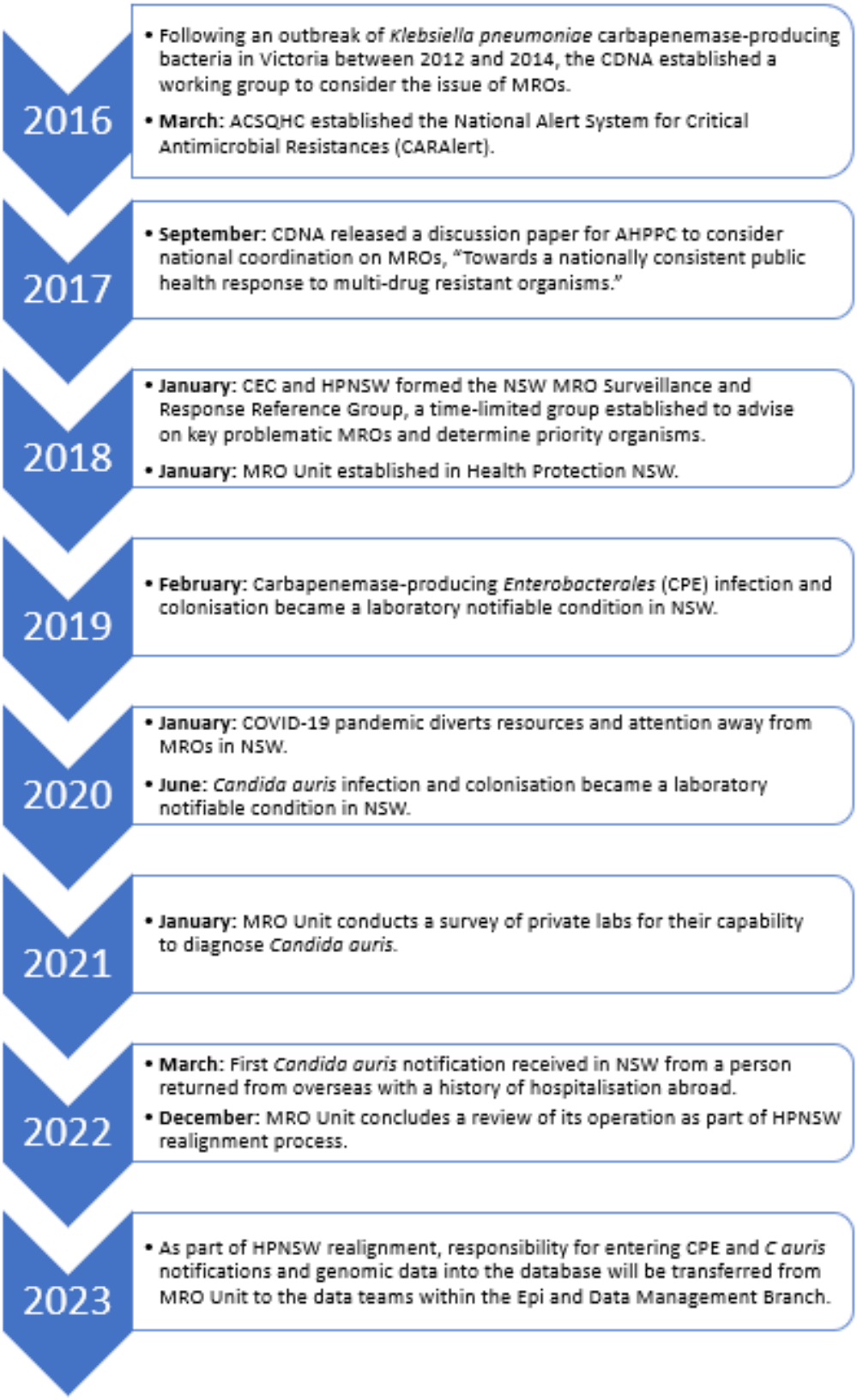
The objectives of the evaluation of the MRO surveillance system in NSW were to:

- Describe the operation of the system;
- Review the stated objectives of the system and its performance against those objectives;
- Assess the performance of the surveillance system according to key attributes;
- Identify and articulate the challenges encountered; and
- Make recommendations for implementation and improvement.

## Methods

I used the CDC's Updated Guidelines for Evaluating Public Health Surveillance Systems as a framework for the evaluation.[60] I identified key stakeholders involved in the surveillance system through consultation with supervisors, including the NSW Health MRO epidemiologist and MRO medical advisor, the Acting Directors of the Communicable Diseases Branch, and the Executive Director of HPNSW. I reviewed the notifications collected by the system from its creation in February 2019 to 30 June 2023 and conducted eight key informant interviews. I also participated in various aspects of MRO surveillance, including joining the AMR genomics meetings and outbreak meetings, drafting the standard operating procedure for notifications and a handover document for the MRO Unit, supporting with entry of notifications into the surveillance database, and liaising with NSW Health Pathology – Institute of Clinical Pathology and Medical Research (ICPMR) to collect whole genome sequencing (WGS) information. I created the schematic diagram showing how the system operates from specimen collection to complete notification.

Figure 1: Timeline of key events in NSW MRO surveillance system



## Results

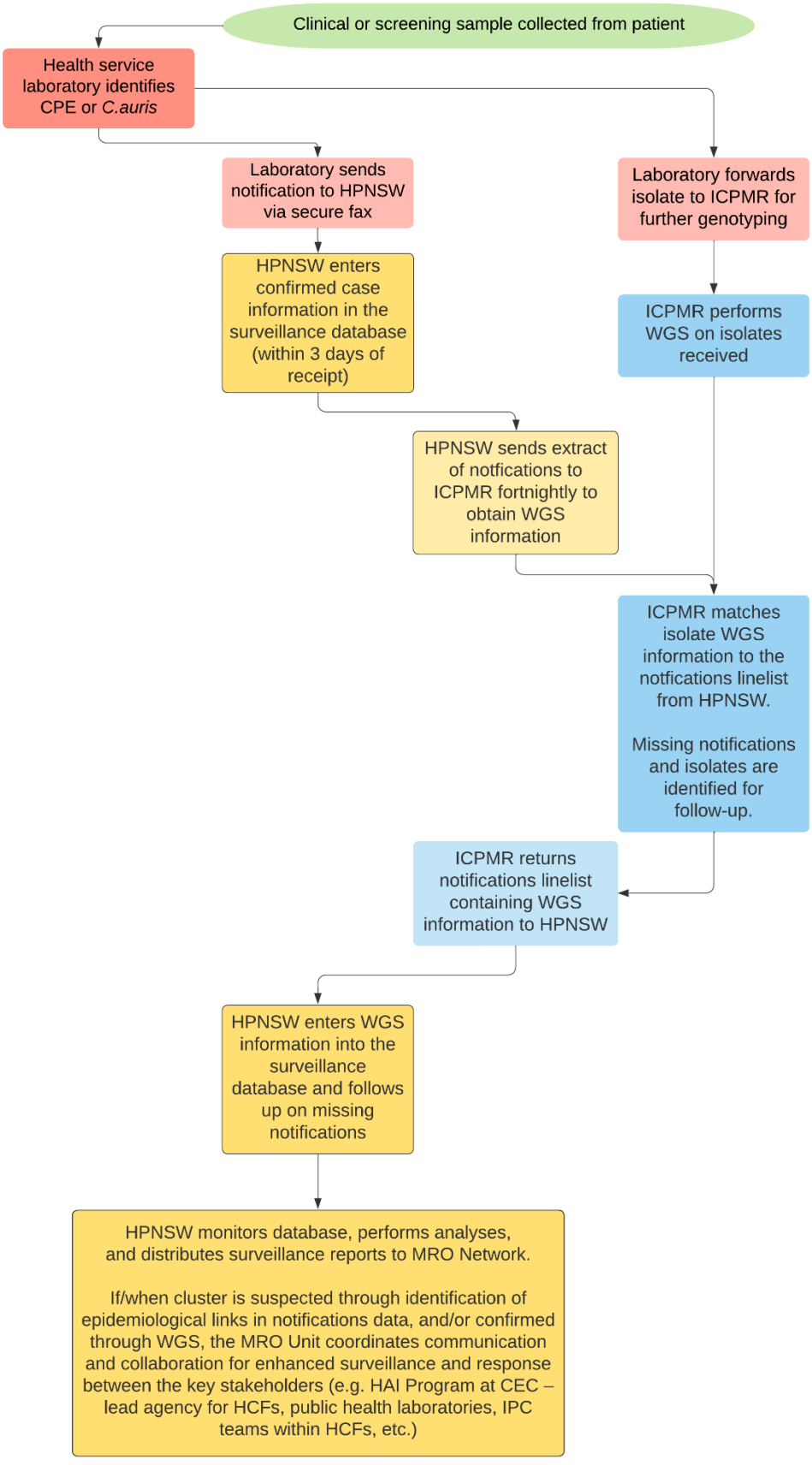
### Description of the system

The MRO surveillance system is administered by HPNSW using CPE and *C auris* notifications received under mandatory reporting of notifiable conditions. Notifications are received via fax from laboratories, and manually added by a member of the MRO Unit to the CPE or *C auris* Excel spreadsheet database in the secure file network of HPNSW. Positive isolates are forwarded by the notifying laboratory to ICPMR at Westmead for WGS and bioinformatics analysis. This analysis allows characterisation of the resistance genes, monitoring of levels of resistance and diversity of resistance genes, and identifies related isolates and clusters. Genomic information for notified cases is sent to HPNSW by secure file transfer, where it is added to the surveillance database. HPNSW and ICPMR produce fortnightly surveillance reports showing analysis of notification trends and genomic clusters. The reports are distributed to IPC teams in NSW Health facilities via the CEC, and to the Health Protection Leadership Team (Directors of all NSW Public Health Units) for awareness. The report is discussed at fortnightly meetings between HPNSW, ICPMR, other laboratories, and CEC.

Case investigations and follow up are conducted directly by health facility IPC teams and is outside of the scope of the surveillance system. Treating clinicians and IPC teams receive notifications directly from the laboratory and subsequently do not rely upon the MRO surveillance system to conduct their work. When clusters or outbreaks are identified by genomic analysis, this information is passed to the CEC, who liaise with affected facilities to conduct outbreak investigations, including additional screening, active case finding, environmental investigations, and reviews of IPC measures. HPNSW is not responsible for outbreak investigations of CPE or *Candida auris*.

Figure 2 provides a schematic diagram of the operation of the MRO surveillance system in NSW.

Figure 2: MRO Surveillance system in NSW: diagram of operation



### System governance and resourcing

The MRO Unit was established within HPNSW in January 2018. Recruitment of staff to the MRO Unit began in 2018 and continued in 2019. The Unit was planned with five staff positions: a Director of MROs, a medical officer, an epidemiologist, a surveillance officer (role to be filled on rotation by NSW Public Health Officer trainees), and a laboratory liaison officer (infectious disease or microbiology registrar).

However, in early 2020 the arrival of COVID-19 in Australia saw resources diverted, particularly laboratory genomics resources and infection prevention and control resources. All staff who had been recruited to the MRO Unit were redeployed to the COVID-19 response. The epidemiologist was the only staff member who returned, initially every second week from mid-2020, then full-time in October 2020. A new medical officer joined the Unit in November 2020, then left in May 2021. The nascent surveillance system did not grow beyond a passive collection of notifications, standard analyses, and a limited distribution of reports. The NSW MRO Surveillance and Response Reference Group has expired.

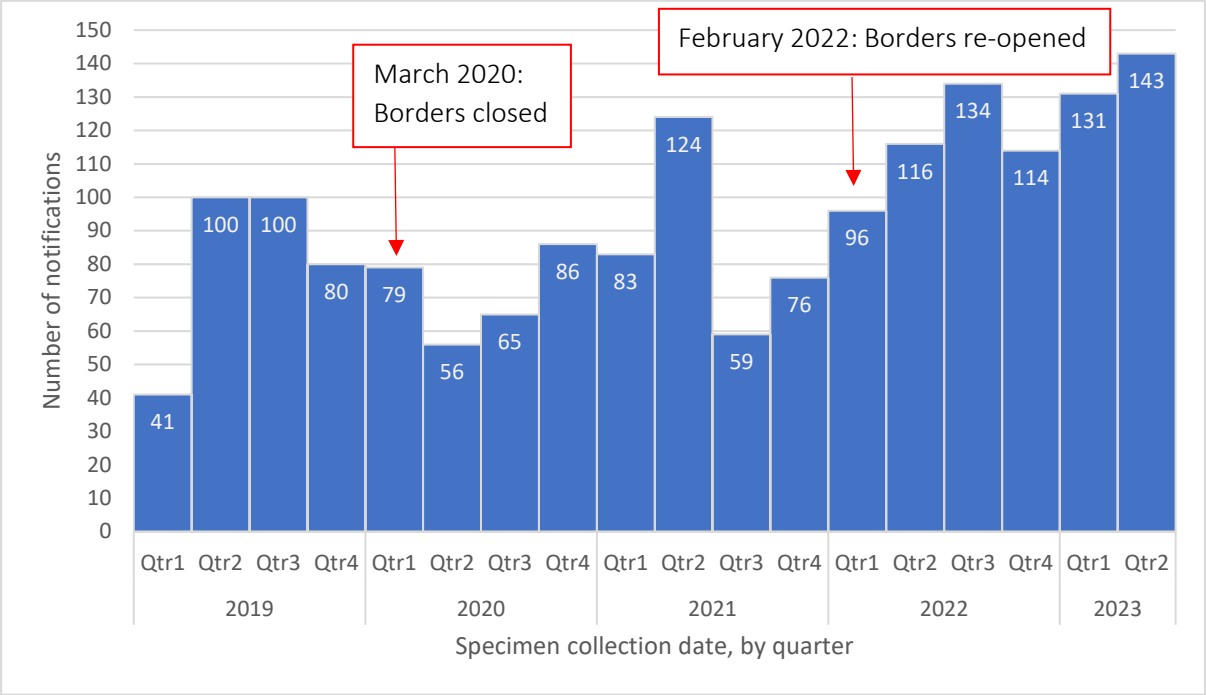
## Objectives of the system

The stated objective of the surveillance system is "to monitor the epidemiology of carbapenemase-producing *Enterobacterales* (CPE) to inform prevention strategies and support control strategies."[61] The NSW Ministry of Health wished to understand the extent to which CPE was present in the NSW population and identify the level and location of any CPE transmission occurring in NSW. Key questions included: what were the main CPE organisms and resistance genes present in NSW? Was CPE endemic or driven by overseas importation? Was CPE at a level in NSW where it could be contained with additional resources and more targeted prevention and control strategies? What would these look like? Existing surveillance of MROs through the CEC's healthcare acquired infection surveillance system was limited to nosocomial infections in acute care health services. The intention of making CPE notifiable was to expand the sources of data and get a better view of CPE at state level.

The arrival of the COVID-19 pandemic in early 2020 and the subsequent closure of Australia's international, and later, state borders provided a natural experiment of the contribution of overseas importation to CPE rates. On 20 March 2020 Australia's borders were closed to all non-citizens and non-residents and on 24 March 2020 Australian citizens in Australia were banned from travelling overseas.[62] Australian citizens were able to return to Australia throughout this period with a compulsory two-week hotel quarantine. International borders were reopened to fully vaccinated visa holders on 21 February 2022.[62] Over this period of border closures CPE notifications remained steady,

with no discernible impact from the dramatic reduction in international arrivals and overseas travel by Australians (Figure 3). It is now apparent that CPE is endemic in NSW. Making CPE notifiable in NSW, together with the natural experiment of the extended border closures, has enabled this observation.

**Figure 3: Epidemiological curve of CPE notifications, by specimen collection date, NSW, 28 February 2019–30 June 2023. The close and re-opening of international borders are indicated in red.**

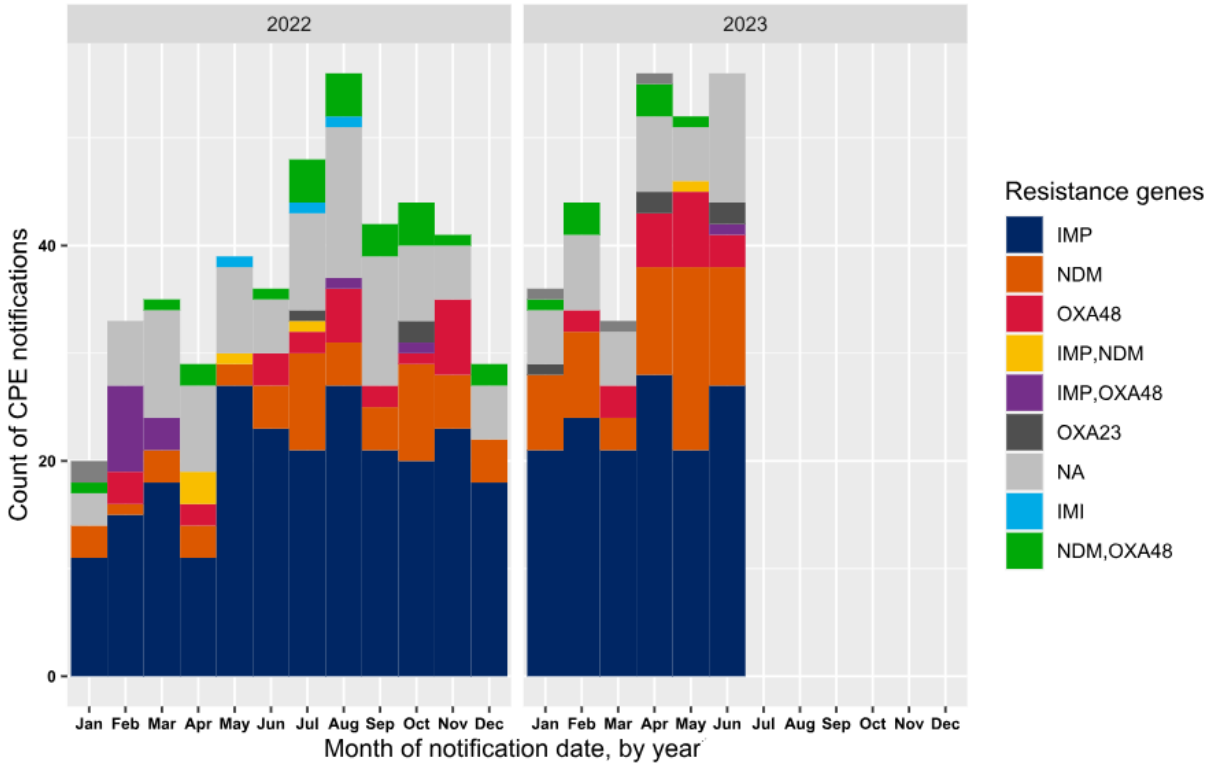



The first case of CPE was notified 5 March 2019 and to 30 June 2023 the surveillance system has detected 1,683 CPE events and two *Candida auris* events. The majority of CPE cases were identified in acute health care services, however, cases have also been detected in community settings.

Both notified *C auris* cases had recent history of hospitalisation in India, one for a liver transplant and the other for an unknown reason. Both cases were also positive for CPE. One case sadly passed away shortly after their *C auris* diagnosis.

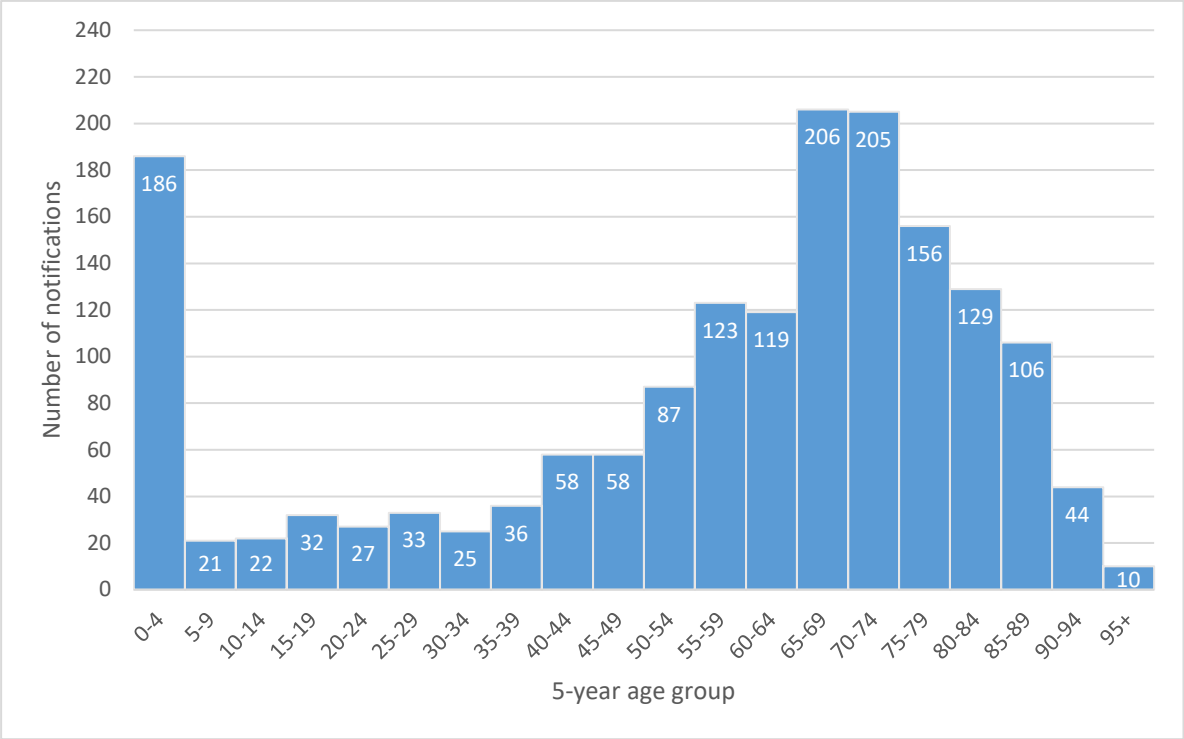
The most commonly identified organism in CPE is *Enterobacter hormaechei*, followed by *Escherichia coli*, *Klebsiella pneumoniae*, and *Citrobacter freundii*. The most common resistance gene identified in NSW notifications is $bla_{\text{IMP-4}}$, which confers the ability to produce imipenemase, $bla_{\text{NDM-5}}$, which confers the ability to produce New-Delhi-metallo-β-lactamase, and $bla_{\text{OXA-181}}$, which confers the ability to produce oxacillinase (Figure 4).

Figure 4: Graph of resistance genes identified in NSW CPE notifications 01 January 2022 to 30 June 2023. This graph has been produced by Keren Francis, MRO Team, from the internal *Carbapenemase-Producing Enterobacterales Fortnightly Surveillance Report: NSW*, using adjusted dates.




The surveillance system collects information on age, sex, residential address, date and place of specimen collection (health care facility and ward), type of specimen (e.g. urine, blood, nasopharyngeal swab, rectal swab) and notifying laboratory for CPE cases. Beyond these demographic and specimen details, the system does not collect any information about hospitalisation history or movements between facilities or wards, co-morbidities, current hospitalisation or treatment history such as the presence of indwelling devices or recent invasive procedures, or any travel history. The available information on CPE epidemiology in NSW is thus limited. To 30 June 2023 58% of CPE notifications have been in males. Notifications are clustered in the older age groups 55 years and above and in very young children. The highest number of notifications have been received for people aged 65-69 years and 70-74 years, followed by children aged 0-4 years (Figure 5). The high numbers of notifications in the 0-4 year age group result from a number of clusters of CPE with $bla_{\text{IMP-4}}$ resistance gene identified in neonatal units, with 127 notifications in infants under 12 months of age.

Figure 5: CPE notifications by 5-year age group, NSW, 28 February 2019–30 June 2023.




## System attribute evaluation

### Usefulness

The CDC guidelines state that a public health surveillance system is useful "if it contributes to the prevention and control of adverse health-related events, including an improved understanding of the public health implications of such events."[60] The NSW MRO surveillance system has provided useful information about the magnitude of CPE in NSW, the types of organisms and resistance genes involved, the location of cases and clusters, and answered the question of CPE endemicity. The system has generated information to support the conclusion that CPE is an important adverse health-related event in NSW. Despite shortcomings in the system, it has proven useful to monitor the epidemiology of CPE in NSW. Its usefulness to inform prevention strategies has been hampered by the lack of enhanced surveillance data collection. The system does not routinely collect information about risk factors for CPE acquisition. Its usefulness to support control strategies is also limited. While genomic analysis is essential for detecting outbreaks and clusters that involve more than one facility, the timeliness of this information feedback and the disconnect between the state-wide surveillance system and the facility IPC teams actioning the initial patient CPE lab detections means it is rarely used as part of control activities.

### Acceptability

The attribute of acceptability reflects the willingness of individuals and organisations to participate in the surveillance system.[60] Laboratories with in-house WGS capacity do not routinely refer MRO isolates to the reference laboratory at ICPMR for WGS. This may be due to a number of reasons, including concerns about the timeliness of isolate processing, concerns about ownership of WGS data, issues with resourcing or funding at the originating laboratory, the extra work involved in referring isolates to ICPMR, or lack of understanding or awareness of the requirement to refer all MRO isolates to ICPMR for WGS. Some of these laboratories submit in-house generated WGS data to the surveillance system, however, as sequences have been generated on different platforms it limits the comparability of sequences. Issues with inter-laboratory referrals in NSW are not unique to MROs and are part of a broader picture of laboratory funding and cooperation. Nonetheless, the hesitancy to fully participate in the MRO surveillance system does indicate a limitation to its acceptability.

### Simplicity

Simplicity refers to both the structure of the surveillance system and its ease of operation, while still meeting the system's objectives.[60] The MRO surveillance system is not integrated into any other surveillance or reporting system. The notifications are not sent to the NSW Notifiable Conditions Information Management System (NCIMS) via electronic laboratory reporting (ELR), unlike other notifiable condition laboratory reports. Notifications must be sent manually to HPNSW, either via fax or secure email. Notifications are not recorded in NCIMS, but in a separate database in an Excel spreadsheet, and must be manually entered into this database by a member of the MRO Unit. This lack of automation introduces complexity into the system, makes the system more difficult to use, and introduces greater potential for error or missed notifications, particularly with the manual entry of all notification data into the system. There is a burden on system users outside of HPNSW to input data into the MRO surveillance system, either in completing the notification forms at the laboratories, completing spreadsheets for data upload, responding to data input queries via email, or other data input activities. A positive CPE result in a laboratory requires the staff member there to inform the attending infectious diseases clinician and the IPC team, complete and fax a notification to the MRO surveillance system, organise referral of the isolate to ICPMR for WGS, and completion of a CARAlerts notification. This results in around 20 minutes of work for the lab staff member per positive result.

### Data quality

Data quality relates to how accurately the data in the surveillance system describe CPE or *Candida auris* cases and clusters. In order to have good data quality the data must be reliable and complete.[60] MRO surveillance data quality is challenged by its manual input, which introduces greater potential for

error, inconsistency or duplication. Respondents reported failed fax transmissions resulting in notifications going missing. The CPE surveillance data are 100% complete for age and 99.9% complete for sex (two notifications with sex missing). Completeness falls to 92.5% for local health district of residence and 68.9% for ward (when notification comes from a sample collected in hospital). Without information about the ward, surveillance data have limited utility to identify patterns of notifications that may indicate clusters or IPC problems in particular wards.

### Sensitivity

Sensitivity is the ability of the surveillance system to detect true cases and outbreaks.[60] There are few studies that offer prevalence or incidence estimates of CPE in the general population, making comparisons between true cases and surveillance notifications difficult. One key respondent who has been involved with the system since its creation and has expert knowledge of CPE estimated the sensitivity of the system as 20%. Their expert opinion is that the system likely misses the vast majority of CPE in NSW. They acknowledged the difficulty of sensitivity estimates without an agreed denominator. The MRO surveillance system has been able to detect clusters of CPE cases linked across facilities by genomics that would otherwise not have been detected.

### Representativeness

Representativeness describes how well the cases detected by the surveillance system represent the distribution of true cases over time by person and place.[60] In the absence of overall testing data an assessment of representativeness is difficult to make. CPE testing, and subsequently CPE notifications, are drawn from a limited group of people who are mostly hospitalised for acute care. The relative absence of CPE testing in community settings seriously limits our understanding of overall prevalence and incidence as well as risk factors leading to colonisation.[12] The MRO surveillance system routinely misses potential cases outside of routinely screened wards, and in high-risk community settings such as residential aged care facilities. People with lower rates of hospitalisation, such as those aged 15-44 and those with fewer co-morbidities, will not be tested for CPE at the same rate as those who are older, in poorer health, and more frequently hospitalised. Differences in screening practices, driven by local priorities and resourcing, may additionally impact the geographic distribution of CPE notifications in NSW. Differences in access to care and subsequently hospitalisations in rural and remote areas, together with fewer tests conducted, may result in lower rates of CPE detection in different parts of NSW.

### Timeliness

Timeliness reflects the time taken between steps in a public health surveillance system.[60] The median time between specimen collection and notification to the system was 5 days (IQR 3–10). Notifications

are usually entered into the surveillance database within two days of receipt. Once a fortnight the new notifications are sent to ICPMR to match with the sequencing data, and a surveillance report is prepared. The report is discussed at the fortnightly MRO surveillance meetings and distributed to a restricted list of stakeholders.

The lack of ELR and exclusion of CPE from NCIMS is a barrier to timely reporting of notifications, as is the need to manually and separately solicit genomics data and match these back to the notifications. Treating clinicians and facility IPC teams receive notifications directly from the laboratory and are able to treat patients accordingly and initiate control and prevention measures in their facilities irrespective of the notification process. On average, CPE data analysis outputs (e.g. genomics reports, cluster alerts) take between three to four weeks to be distributed from the state-wide MRO surveillance system after a patient tests positive for CPE.

#### Stability

Stability refers to the reliability and availability of the surveillance system.[60] The operation of the MRO surveillance system is highly dependent upon the availability of certain individuals, and therefore can be significantly affected by periods of leave, illness, individual capacity, or people changing jobs. It also relies upon a set of processes that are not integrated into other communicable disease surveillance systems, and thus are more reliant upon individuals to take actions, rather than automated systems of notification.

## Discussion

### The NSW MRO surveillance system: a square peg in a round hole

MROs and AMR have traditionally been viewed as a health facility issue to be managed by health facility IPC teams. Prior to the establishment of the MRO surveillance system and the addition of CPE and *C. auris* to the list of notifiable conditions in NSW, all surveillance of MROs had been conducted through this lens of nosocomial infection surveillance via the CEC's surveillance of healthcare associated infections in NSW public acute care services. This system uses 10 mandatory clinical indicators for routine surveillance of HAIs, including carbapenemase-producing *Enterobacterales* blood stream infection and clinical isolates, and other MROs.[63] The mandatory clinical indicators have clearly defined areas of responsibility, surveillance and response actions for facilities, and reporting lines through Local Health Districts (LHDs) to the CEC and the Ministry of Health. HAI surveillance data in this system is systematically collected and analysed. However, by focusing only on CPE HAIs the system does not provide accurate information about the burden of CPE in NSW, as it excludes CPE

notifications in people outside of hospitals and excludes CPE detections that are deemed to be colonisations. Information about CPE that is detected on admission screening is used for internal infection risk assessments and not shared beyond the facility.

At a national level, control of MROs is incentivised through various pricing levers, including the National Health Reform Agreement which incorporates safety and quality measures into the pricing and funding of public hospital services in Australia, and accreditation levers, such as the Australian Health Service Safety and Quality Accreditation Scheme. The Independent Health and Aged Care Pricing Authority (IHACPA) and the ACSQHC have developed a list of hospital acquired complications, which include healthcare acquired infections with MROs, and IHACPA uses an adjustment algorithm to reduce federal funding for any episode of admitted acute care where a hospital acquired complication occurs.[64, 65] All jurisdictions endorsed these pricing and funding for safety and quality mechanisms via the Addendum to the National Health Reform Agreement. Under the Australian Health Service Safety and Quality Accreditation Scheme, health service organisations are assessed against a set of standards, including the National Safety and Quality Health Service Standards, of which Standard 3 is Preventing and Controlling Infections.[66] This standard mandates a set of actions around surveillance, antimicrobial usage, and infection prevention and control measures that health service organisations must take to meet the standard for accreditation. Accreditation is a pre-requisite for operation as health service in Australia. Through these regulatory and pricing levers, the surveillance and control of MROs are highly incentivised.

However, in this environment of financial and regulatory consequences for HAIs, and with surveillance of MROs occurring almost exclusively in health facility settings and being seen as a health facility problem, there is a level of stigma associated with MRO infections, and therefore a reluctance to share data or openly discuss the problem, especially across facilities or health districts. HAIs are seen as a 'failing' of the health service and are a sensitive issue.

Into this environment Health Protection NSW launched its MRO surveillance system, using the model of communicable disease surveillance via mandatory laboratory notifications that has been implemented for other infectious diseases. This system detects and records colonisations, and in fact is often unable to distinguish between a colonisation or an infection without adequate information about the specimen type, and no information collected about past medical history, reason for admission or reason for testing. Without collecting any enhanced surveillance data such as travel or hospitalisation history, the system is not able to monitor CPE transmission in NSW. Plans to pilot enhanced surveillance data collection for CPE were shelved when the COVID-19 pandemic began, and resources were too stretched. While the system collects all notifications regardless of origin (hospital or community), CPE testing is predominantly conducted as a screening exercise on admission to

specific wards in acute health care facilities, or when clinically indicated for a patient in an acute health care facility. The system has poor coverage of other long-term residential settings and community settings. There is no consensus on screening guidelines or criteria between facilities. As a result of highly variable screening practices across facilities and LHDs, prevalence also varies widely, and CPE notification data cannot be meaningfully analysed by place.

When the NSW surveillance system detects a cluster of CPE cases using genomic analysis, it advises the CEC, who then reach out to the IPC team in the affected health facility or facilities. Management of the cluster is the responsibility of the facilities, in liaison with the CEC. Often the affected facilities are already aware of the cases. Beyond notifying the CEC of clusters, there are no public health actions that arise from the data collected by the surveillance system.

The role of HPNSW in the MRO surveillance system is limited and passive. The data collected are not useful for epidemiological analysis, do not provide information about transmission in NSW, and thus cannot be used to inform or evaluate control measures. The data is not provided back to the system users in a timely or accessible manner. The MRO surveillance system runs parallel to the CEC's 10 mandatory clinical indicators for routine surveillance of HAIs and produces partially overlapping data. The design of the MRO surveillance system, without enhanced data collection or the resources required to conduct analysis beyond genomics, severely limits its utility as measure to combat AMR in NSW.

Ambiguity about 'ownership' of state-wide AMR surveillance, strategy, and response hampers system improvement. The CEC has responsibility for HAI surveillance, antimicrobial stewardship, and AMR policy in NSW, and has worked with facilities to establish standards and practices over many years. However, the CEC has no capacity or mandate to extend MRO surveillance beyond HAIs and acute care facilities. HPNSW has no technical leadership in AMR, and no coordinated program of AMR surveillance. Public health actions for LHDs and public health units (PHUs) are unclear and the involvement of PHUs in CPE surveillance varies by individual capacity and prioritisation. Rather than complementing or enhancing the existing MRO surveillance structures of the CEC, HPNSW's intervention in this space adds a duplicative layer without addressing the actual gaps in surveillance.

The system of isolate referral for genotyping is similarly plagued by governance and ownership issues. Some laboratories with the capacity for WGS prefer to conduct this in-house and share sequencing data, rather than sending isolates to ICPMR. This means that WGS is conducted on different platforms, and WGS data must be solicited from multiple laboratories.

## The role of genomics in MRO surveillance

Genomics is changing the landscape of public health surveillance and outbreak response in many domains, including foodborne bacterial pathogens, tuberculosis, influenza, and antimicrobial resistance. [67] AMR and MRO surveillance using WGS has allowed precision identification of organisms and genes that convey critical resistance, permitting faster and more targeted treatments for patients.[68] In NSW, WGS has rapidly expanded as an important tool for public health management of communicable disease outbreaks and is routinely performed as part of CPE surveillance and outbreak investigation in NSW. WGS and genomic analysis has been used to identify clusters of CPE and facilitate rapid identification of resistance patterns in the implicated bacteria.

## The impact of the COVID-19 pandemic

Emerging evidence both in Australia and internationally suggests that hospitalisation for COVID-19 illness in high care or ICU settings creates an optimal environment for nosocomial infections and colonisations with MROs.[69-74] This is due to these high dependency patients frequently requiring ventilation, a reduction in MRO screening protocols, increased demands on staff leading to a reduction in safe hand hygiene practices, and changes in PPE use.[73, 74] A detection of CPE in an ICU caring exclusively for COVID-19 patients in a tertiary metropolitan hospital in Sydney during the SARS-CoV-2 Delta variant outbreak in 2022 led to active surveillance and a review of IPC measures.[73] The study found that several factors had created an ideal environment for CPE to flourish. A reduction in MRO screening due to overwhelming workloads in both the ICU and the laboratory as a result of the COVID-19 surge impacted the timeliness of the detection of CPE on the ward, and subsequently the initiation of IPC measures.[73] Demands on staff providing labour-intensive multi-person care for acutely unwell COVID-19 patients in a cohort setting, including intubations, inserting lines and catheters, and close manoeuvres such as rolling patients for prone nursing, together with a suspension of hand hygiene audits and reduction of non-COVID IPC measures provided an environment in the ward that was conducive to CPE transmission between patients.[73] Finally, use of increasingly broad-spectrum antibiotics to treat patients with COVID-19 pneumonitis likely contributed to selection for resistant organisms.[73] It is likely that the experience in this ICU was replicated in many other healthcare settings during the COVID-19 pandemic. Conversely, an increased focus on PPE and IPC measures overall, together with reduced movement due to lockdowns, may have limited spread of CPE in some settings.[74]

With the closure of Australia's international border during the COVID-19 pandemic and commensurate dramatic reduction in overseas arrivals, the threat of importations of CPEs and *C. auris* was diminished, however, this was expected to change when international and domestic borders re-

opened, and travel resumed at pre-pandemic levels. As a result of the long closure of Australia's international border during the COVID-19 pandemic, many Australian citizens and residents have experienced prolonged stays out of Australia, and some will have been hospitalised abroad for COVID-19 and other illnesses or injuries. The return of these individuals to Australia represented a significant potential introduction of people colonised with MROs. However, the closure and re-opening of Australian borders had no discernible impact on CPE notifications. This may be due to weakness of the system to detect cases outside of specific screening environments.

Broader impacts of the COVID-19 pandemic on MROs and AMR surveillance in Australia are harder to identify. Interviewees in this evaluation reported positive impacts, such as advances in data sharing and cooperation between states, territories and the Commonwealth, and the rise of genomics and investment in genomics capacity and collaborations. An increased awareness of the value of IPC and public health resulted in additional resourcing. However, COVID-19 also highlighted the different approaches of states and territories to health issues, particularly in our jurisdiction-based health system, and one interviewee suggested that disagreements over priorities and direction during the COVID-19 response had left those relationships more distant and hindered cooperation.

## Conclusions

The surveillance system is moderately useful as a source of information about the prevalence of CPE in NSW, although the data it produces are not representative and the sensitivity of the system is poor. The system is further weakened by its partial duplication of other MRO surveillance systems that measure HAIs, and lack of integration into electronic lab notification and routine surveillance systems used in NSW. The system is manual, additionally complex, and lacks stability or universal acceptability. The data it produces are not returned to the system users in a timely fashion. Without enhanced surveillance data, the system has limited ability to identify transmission or inform strategies to control MROs in NSW.

## Summary of recommendations

The MRO surveillance system in NSW is at a critical juncture. In its current format the system is not meeting its objectives, is providing only limited information about CPE in NSW, and is not contributing towards prevention or control strategies. The system either requires significant investment and restructuring to improve, or MRO surveillance should be rehoused in an existing and more appropriate surveillance system. The first step in this decision is to undertake a mapping exercise to understand

the landscape of MRO surveillance and data collection in NSW, and the agencies and organisations involved, and to re-establish the NSW MRO Surveillance and Response Reference Group to advise on the strategy and direction of MRO surveillance in NSW. Once the scope and objectives of MRO surveillance in NSW have been redefined, a decision can be made about the future of the current system. If it is decided to retain the current MRO surveillance system, I propose the following recommendations to strengthen the system and improve its usefulness in NSW:

1. Resource the MRO Unit appropriately, at the level originally planned prior to the COVID-19 pandemic.
2. Draft terms of reference or memoranda of understanding between CEC, HPNSW and NSW Health Pathology to clearly define roles and responsibilities.
3. Establish agreed surveillance objectives and indicators, and public health actions arising from surveillance data.
4. Re-establish the MRO network meetings.
5. Replace the manual notifications process with ELR-based system that can incorporate phenotypic and WGS data.
6. Finalise case definition & guidelines for *C.auris*.

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# CHAPTER 5

## Analysis of a public health dataset

The arrival of Omicron in NSW: Analysis of first cases and comparison with Delta

## Chapter 5: Table of contents

## List of abbreviations

| | |
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| CDB | Communicable Diseases Branch |
| CDNA | Communicable Diseases Network Australia |
| GP | General Practitioner |
| HPNSW | Health Protection NSW |
| LHD | Local Health District |
| MoH | Ministry of Health |
| NCIMS | Notifiable Conditions Information Management System |
| NSW | New South Wales |
| PFP | Patient Flow Portal |
| PHRB | Public Health Response Branch |
| PHU | Public Health Unit |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoNG | Series of National Guidelines |
| VE | Vaccine effectiveness |
| VOC | Variant of Concern |
| WHO | World Health Organization |

## Preface

This chapter presents a descriptive analysis of the epidemiology and clinical outcomes of the first three weeks of confirmed cases of the SARS-CoV-2 Omicron variant of concern (VOC) in NSW, from 27 November to 17 December 2021, and a comparison of Omicron VOC cases with Delta VOC cases occurring in the same study period. This chapter addresses the following competencies:

- Analysis of a public health dataset

## My role

This data analysis project is an expanded analysis that has built on a series of rapid analyses conducted during the Omicron outbreak in December 2021 and January 2022. In an outbreak setting it is important to be able to conduct real time analysis and generate information for action. The initial analysis used Excel and was conducted in conjunction with my colleague Sarah Alland in the Public Health Response Branch (PHRB). The results that we generated were rapidly shared with the PHRB executive to improve understanding of the Omicron variant and its impact on the landscape of the SARS-CoV-2 pandemic in NSW.

I chose to analyse cases occurring in the same time period to control for variables such as vaccination status (same proportion of cases in each group likely to have had the opportunity to be vaccinated), time since vaccination for those vaccinated, non-pharmaceutical interventions (e.g. movement restrictions due to lockdowns), season (late spring/early summer for all cases), and chance of exposure (number of cases in the community and risk of exposure to those cases). This gave my analysis the same population at the same time, exposed to two different variants of concern (VOCs), to examine the effect of those two VOCs on disease severity outcomes.

I wrote the data analysis plan and revised it in line with the scaled back approach. I obtained ethics approval for the study and completed the data request from the Notifiable Conditions Information Management System (NCIMS) surveillance manager and data custodian. I received the full dataset in March 2023 and was able to conduct data cleaning (which was limited in the original rapid analysis) and have access to more information about hospitalisation outcomes. I performed the descriptive analyses again in May and June 2023 with the more complete dataset, using Stata v.17.

## Key reflections

Linking the NCIMS data to the Patient Flow Portal (PFP) data gave me better data quality on outcomes, but also added a lot of data cleaning right down to the individual case level. For example, the NCIMS data contains a yes/no flag for hospitalisation, but with no information about the reason for the hospitalisation. By having the PFP data linked I could access information about admission reason and

ward type. Unfortunately, the admission reason data was a free text variable, and unsurprisingly it was not completed in any standardised way. I was not able to exclude hospitalised cases based exclusively on the ward type, as I learned when I investigated those in the Obstetrics and Gynaecology wards. Some of these cases were admitted for delivery, and most likely screened for COVID-19 on admission and found to be positive. Others had their reason for admission listed as "COVID-19 +" and were perhaps admitted to an Obstetrics ward because they were also pregnant, for better monitoring. I had to work through these groups of hospitalised cases individually to determine which should be excluded from the category "Hospitalised due to COVID-19." Incidentally, I also learned through this process of reviewing reasons for admission that 'cyesis' means pregnant. New word for the crossword!

The addition of the PFP flag for hospitalisation also introduced another element of discrepancy to the data analysis, as some cases that were flagged as hospitalised in NCIMS were not flagged in PFP and vice versa. I discussed the discrepancies between datasets with experts from the epidemiology and data systems teams, the COVID-19 epidemiology team manager and the COVID-19 case interview team leader to help me understand why the datasets were different and which was more accurate. For example, in the original data download, the variable reporting hospitalisation as a binary yes/no outcome in NCIMS gave a figure of 720 hospitalisations, while the variable reporting the same outcome in the Patient Flow Portal dataset gave a figure of 320 hospitalisations. I learned that the NCIMS figure was likely to be more accurate, as this data point in NCIMS was completed by the person conducting, or attempting to conduct, the case interview. Although this did mean that some cases were recorded as hospitalised when their hospitalisation was not due to COVID-19, it was a better starting point for my data cleaning than the Patient Flow Portal variable, which was likely to be an undercount due to matching problems linking PFP data back into NCIMS. Any discrepancies between the patient details recorded in PFP (e.g., name spelled differently, date of birth recorded incorrectly, different address given) would result in the PFP hospitalisation result not matching to the NCIMS case ID, which was the variable used to link the two datasets.

I had initially planned to analyse symptom data for all cases in the study, to examine any differences in symptom profile between Delta and Omicron VOC cases. I requested this data and received the symptom variables in the dataset, however, as I started data cleaning, I discovered all symptom observations were missing. I went back to the data team, who suggested the reason for this was an incorrect data extraction and re-ran the extraction in a different way. The new dataset had observations, but these were all "no" for every symptom variable. This was a surprise and a puzzling discovery for the data team. I went back to the COVID-19 case interview team leader, who fortunately still works in Health Protection NSW, and learned that symptom data was in fact not being collected

during this period. It was only in March 2022 when NSW shifted to selective case interviewing and direct electronic case interview data capture that symptom data were routinely collected in each case interview. Prior to this it had been collected sporadically in paper case interview forms. As cases increased rapidly with the arrival of Omicron, the priority in case interview was to identify contacts and enact measures to limit onward transmission. Symptom data was not considered important, and the escalating case interview workload meant these questions were left out. Despite the interest in differential symptom profiles between VOCs, this data was not being collected. This was an important lesson to learn about the disconnection and assumptions made by different parts of the surveillance system and end users of that data.

## Public health impact

Preliminary and rapid analyses for this project were conducted in real time in December 2021 and January 2022 and informed the surveillance and responses to the Omicron VOC outbreak in NSW.

## Acknowledgements

Thank you to Sarah Alland, David Muscatello, Travers Johnstone and Janaki Amin for their help on the first rapid analyses, the development of the first formal project proposal and data analysis plan, and securing the dataset for the expanded analyses. A special thank you to Liz Walker for the life-saving project proposal surgery.  Thank you to Roy Byun and Alicia Arnott for COVID-19 diagnostics discussions and advice.

## Ethics

Ethics approval was granted by the Australian National University Human Research Ethics Committee under protocol 2022/289.

## Abstract

### Background

On 24 November 2021 South Africa reported the identification of a new SARS-CoV-2 variant, B.1.1.529, to the World Health Organization (WHO), which was subsequently named Omicron and designated as a variant of concern (VOC). The arrival of Omicron VOC triggered a new wave of SARS-CoV-2 infections around the world, and this variant demonstrated increased transmissibility and distinct immune evasion characteristics, causing higher rates of breakthrough infections than the previous VOC, Delta. We aimed to characterise the first cases of Omicron VOC in NSW, describe any differences in observed severe disease outcomes between the Delta VOC and Omicron VOC cases occurring in the same time period, and examine the speed and degree to which Omicron VOC replaced Delta VOC as the dominant circulating variant in NSW.

### Methods

We conducted a retrospective cohort study, using three weeks of case notifications from the date of first Omicron VOC case specimen collection (27 November 2021 to 17 December 2021) and 28 days of follow-up for all cases for outcomes. Based on either Whole Genome Sequencing, or an original PCR test result recording an S gene dropout/S gene target failure, we assigned cases to one of four categories (Confirmed Omicron, Probable Omicron, Confirmed Delta, Probable Delta). We examined disease severity using three outcome measures: hospitalised due to COVID-19, admitted to ICU, and died due to COVID-19. We described the cohort using demographic, vaccination, geographic and clinical outcome information.

### Results

We included 5,163 cases in the descriptive analysis: 2,812 (54.5%) were confirmed or probable Delta cases (collectively known as “Combined Delta”) and 2,351 (45.5%) were confirmed or probable Omicron cases (collectively known as “Combined Omicron”). The rate ratio of male to female cases was 1.10 in the Combined Delta group and 0.99 in the Combined Omicron group. The age distribution of Omicron VOC cases differed greatly to Delta VOC cases, with the rate of Omicron VOC cases in the 20–24 year age group more than 2.5 times higher than the rate for Delta cases. We observed lower rates of vaccination among the Delta VOC group compared to the Omicron VOC group and consequently higher rates of breakthrough infections in the Omicron VOC group. The Delta VOC group recorded significantly higher numbers of disease severity outcomes than the Omicron VOC group.

Omicron VOC cases were responsible for large increases in COVID-19 case notifications over the study period, and Omicron VOC had replaced Delta VOC as the dominant circulating variant in NSW within 15 days of its introduction into the NSW community.

### Conclusion

Omicron VOC cases drove a spike in case notifications, triggering the largest wave of COVID-19 cases in NSW at the time, and changing the landscape of the outbreak. We observed fewer severe disease outcomes (hospitalisations, ICU/HDU admissions, deaths due to COVID-19) in cases infected with Omicron VOC than in cases infected with Delta VOC, but the reasons for this may relate to the age profile, vaccination status or underlying health conditions of the two variant case groups and cannot be determined by a descriptive study like this one.

## Introduction

On 24 November 2021 South Africa reported the identification of a new SARS-CoV-2 variant, B.1.1.529, to the World Health Organization (WHO). The variant was detected in specimens collected on 11 November 2021 in Botswana and on 14 November 2021 in South Africa.[1] A targeted genomic search of earlier specimens from South Africa subsequently detected B.1.1.529 in specimens collected on 8 November 2021.[2, 3] On 26 November 2021, following advice from the Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE), WHO designated B.1.1.529 a variant of concern (VOC) and named it Omicron.[1]

The detection of the new variant corresponded with a steep increase in the number of cases in South Africa, particularly in Gauteng Province.[1] The seven day rolling average of new daily cases in South Africa was 266 on 8 November, 674 on 23 November, and 5092 on 2 December. Test positivity also increased from 10.3% on 30 November (4,373 cases) to 24.3% on 3 December (16,055 new cases).[3] This surge in cases was the first indication of the potential increased transmissibility of the Omicron variant.[3] Early data from South Africa indicated that Omicron infections were occurring in people who had previously reported SARS-CoV-2 infections, lending weight to concerns of decreased immune response against Omicron.[3]

From a genomic perspective, the early characterisation of the Omicron variant caused particular concern due to the large number of mutations in the S gene. The spike protein of this variant contains at least 30 amino acid substitutions, 15 of which are in the receptor binding domain.[2] As the spike protein is the primary target of vaccine-induced immunity, the number and location of these substitutions raised concerns about potential reductions in effectiveness of available COVID-19 vaccines against this variant.[2]

The first Omicron variant case was reported in New South Wales (NSW) on 28 November 2021 from a specimen collected on 27 November 2021 from a returned traveller from South Africa.

### Diagnosis of Omicron variant

Both Alpha (B.1.1.7) and Omicron (B.1.1.529) VOCs contain mutations in their spike gene, or S gene, including a deletion of two amino acids at position 69 and 70 in the spike protein. This deletion causes the S gene target in a common commercial PCR assay, ThermoFisher's TaqPath COVID-19 assay, to fail.[4] The assay uses three gene targets (ORF1a/b, S and N) and thus it is still capable of reporting a sample positive for SARS-CoV-2 if the assay detects the other gene targets.[5] The S-gene target failure (SGTF) is reported and used as a marker or either Alpha VOC or Omicron VOC.[6]

Very rarely, samples of Delta (B.1.617.2) VOC exhibit SGTF, however, when the prevalence of Alpha VOC or Omicron VOC is high, SGTF is a highly sensitive and specific indicator of either Alpha VOC or Omicron VOC.[4, 7, 8].

In NSW in 2021 the TaqPath COVID-19 assay was in use by Histopath laboratories for SARS-CoV-2 PCR testing. Histopath laboratories operated collection points across NSW and processed approximately 20% of all community samples collected in December 2021 in NSW. These specimens were run on the ThermoFisher TaqPath assay and, if positive, reported as either SGTF or non-SGTF. Although definitive confirmation of any VOC requires whole genome sequencing, in the absence of circulating Alpha VOC, the presence of SGTF allowed a reliable proxy measure of Omicron VOC prevalence. By late December 2021 approximately 95% of Histopath community samples were reported as SGTF.

## Aims and objectives

The aim of the study was to characterise the first cases of Omicron VOC in NSW and the speed and degree to which Omicron VOC replaced Delta VOC as the dominant circulating variant in NSW. The study examined whether people infected with Omicron VOC experienced overall fewer severe disease outcomes than people infected with Delta VOC. The study had two objectives:

1. To describe the epidemiology and clinical outcomes of the first three weeks of confirmed cases of the SARS-CoV-2 Omicron VOC in NSW (27 November to 17 December 2021), and
2. To compare Omicron VOC cases with Delta VOC cases occurring in the same study period.
    a. What was the distribution of SARS-CoV-2 variants in NSW in the first three weeks of SARS-CoV-2 Omicron VOC circulation?
    b. Do people with Omicron VOC experience fewer severe disease outcomes than people with Delta VOC?
    c. Does Omicron VOC cause more breakthrough infections than Delta VOC?

We hypothesised that within three weeks of its introduction into the NSW population Omicron VOC had replaced Delta VOC as the predominant circulating SARS-CoV-2 variant in NSW, that cases infected with the Omicron VOC experienced less severe disease overall (hospitalisations, ICU/HDU admissions, deaths due to COVID-19) than cases infected with the Delta VOC, and that Omicron VOC caused a higher proportion of breakthrough infections (infections in people vaccinated with at least two doses more than 14 days prior to infection) than Delta VOC.

## Methods

We conducted a retrospective cohort study, using three weeks of case notifications from the date of first Omicron VOC case specimen collection (27 November 2021 to 17 December 2021) and 28 days of follow-up for all cases for outcomes. Demographic, epidemiological, vaccination status and laboratory data were extracted from the NSW Notifiable Conditions Information Management System (NCIMS).

Supplementary data on hospitalisation outcomes (including data on reason for admission) were extracted for each case from the Patient Flow Portal (PFP), a tool that captures information about in-patient movements in NSW public hospitals, and matched to the case's data in NCIMS using the unique event ID. New South Wales population estimates by age group and sex were obtained from the Australian Bureau of Statistics.[9] Local Health District population estimates were obtained from Centre for Epidemiology and Evidence, NSW Ministry of Health, via HealthStats NSW.[10]

The study population was all individuals residing in NSW with a laboratory-confirmed SARS-CoV-2 infection reported to NCIMS in the period 27 November to 17 December 2021, who had a case interview completed, acquired their infection in NSW, and had either Whole Genome Sequencing completed, or original PCR test result recording an S gene dropout/S gene target failure, which allowed the case to be assigned to one of the four categories (Confirmed Omicron, Probable Omicron, Confirmed Delta, Probable Delta).

Cases were assigned to one of four categories based on the following case definitions:

- Confirmed Omicron VOC case: laboratory-confirmed SARS-CoV-2 infection where whole genome sequencing (WGS) shows the case to belong to the Omicron (B.1.1.529) variant.
- Probable Omicron case: laboratory-confirmed SARS-CoV-2 infection where WGS is not completed but the PCR test result shows an S gene dropout/S gene target failure, a feature caused by a mutation in the Omicron variant.
- Confirmed Delta VOC case: laboratory-confirmed SARS-CoV-2 infection where WGS shows the case to belong to the Delta (B.1.617.2) variant.
- Probable Delta case: laboratory-confirmed SARS-CoV-2 infection where WGS is not completed but the PCR test result detected the S gene and is thus presumed to be Delta VOC.

We examined disease severity using the following outcome measures: hospitalised due to COVID-19, admitted to ICU, and died due to COVID-19.

Hospitalised due to COVID-19

The binary variable hospitalisation from NCIMS and the Patient Flow Portal were both retrieved for each case. The NCIMS hospitalisation variable was used over the PFP hospitalisation variable due to better data quality in NCIMS. NCIMS records were compiled from patient interviews and represent information obtained directly from cases or their families. PFP data are affected by matching errors from the PFP dataset to NCIMS event IDs.

We generated an overall "Case hospitalised due to COVID-19" variable. All 720 cases flagged as hospitalised in the NCIMS dataset were marked as hospitalised in new variable. Of the 320 cases flagged as hospitalised in the PFP dataset, 310 were also recorded as hospitalised in NCIMS. After discussion with the COVID-19 epidemiology and data manager, the remaining 10 hospitalisations in PFP, which were recorded as missing in the NCIMS hospitalisation variable, were also filled as hospitalised in the new variable.

From this list of 730 hospitalised cases, we used PFP reason for admission data to remove 43 cases with a reason of admission recorded as unrelated to COVID-19 (e.g. maternity, surgery, injury, mental health reasons).

Six cases were excluded from the outcome of "Hospitalised due to COVID-19" when their hospitalisation date preceded the specimen collection date of their positive test and the reason for admission was not listed as COVID-19 or respiratory symptoms, as we are unable to determine if these cases were hospitalised due to SARS-CoV-2 infection or were already in hospital for another reason and had their infection picked up on routine screening.

Admission to ICU

Cases who were admitted to hospital due to COVID-19 and subsequently admitted to an intensive care unit or high dependency unit, indicating more critical condition.

Died due to COVID-19

Cases listed as died due to COVID-19, whether in hospital or in a different location, such as at home or in a residential aged care facility.

## Data cleaning

NCIMS and PFP datasets were linked by the data team performing the data extraction and provided to us as one CSV file. We checked the variable ranges to assess data entry errors and ensure that data fits the correct study period. Events with first notification falling outside of the study period were assessed and removed. Where necessary, we checked original NCIMS event records for correct specimen

collection and notification dates. We re-coded string variables (text) and created new aggregated variables. Where vaccination status was unknown these cases have been treated as unvaccinated.

### Statistical methods

We described the cohort using demographic, vaccination, geographic and clinical outcome information. We described daily notification counts by variant plotted as epidemic curves, and graphed the percentage circulating variant for all cases with known variant. We compared the two groups of cases, Combined Delta and Combined Omicron, using Chi-squared tests. P values $< 0.05$ were considered statistically significant. Analyses were conducted in STATA /IC v17 and figures were made using Microsoft Excel.

## Results

All confirmed cases of COVID-19 in NSW with notification date between 27 November 2021 and 17 December 2021 were extracted from NCIMS. Following data cleaning and exclusions, 13,901 cases remained to be categorised by variant. A further 8,738 cases with variant status unknown were removed, leaving 5,163 cases for the descriptive analysis (Table 1). Of these cases, 2,812 (54.5%) were confirmed or probable Delta cases (collectively known as “Combined Delta”) and 2,351 (45.5%) were confirmed or probable Omicron cases (collectively known as “Combined Omicron”). Figure 1 shows a flow diagram of the study participants.

Figure 1: Flow diagram of NSW COVID-19 cases, 27 November to 17 December 2021

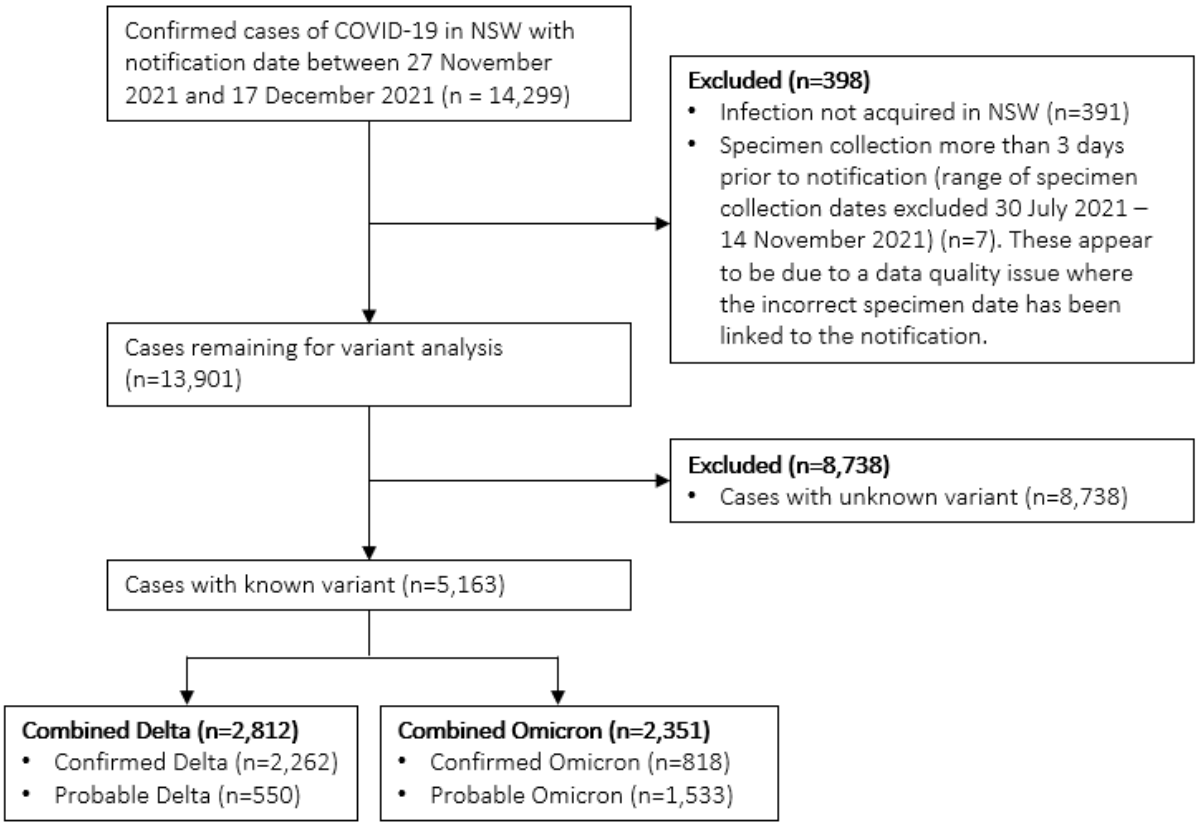


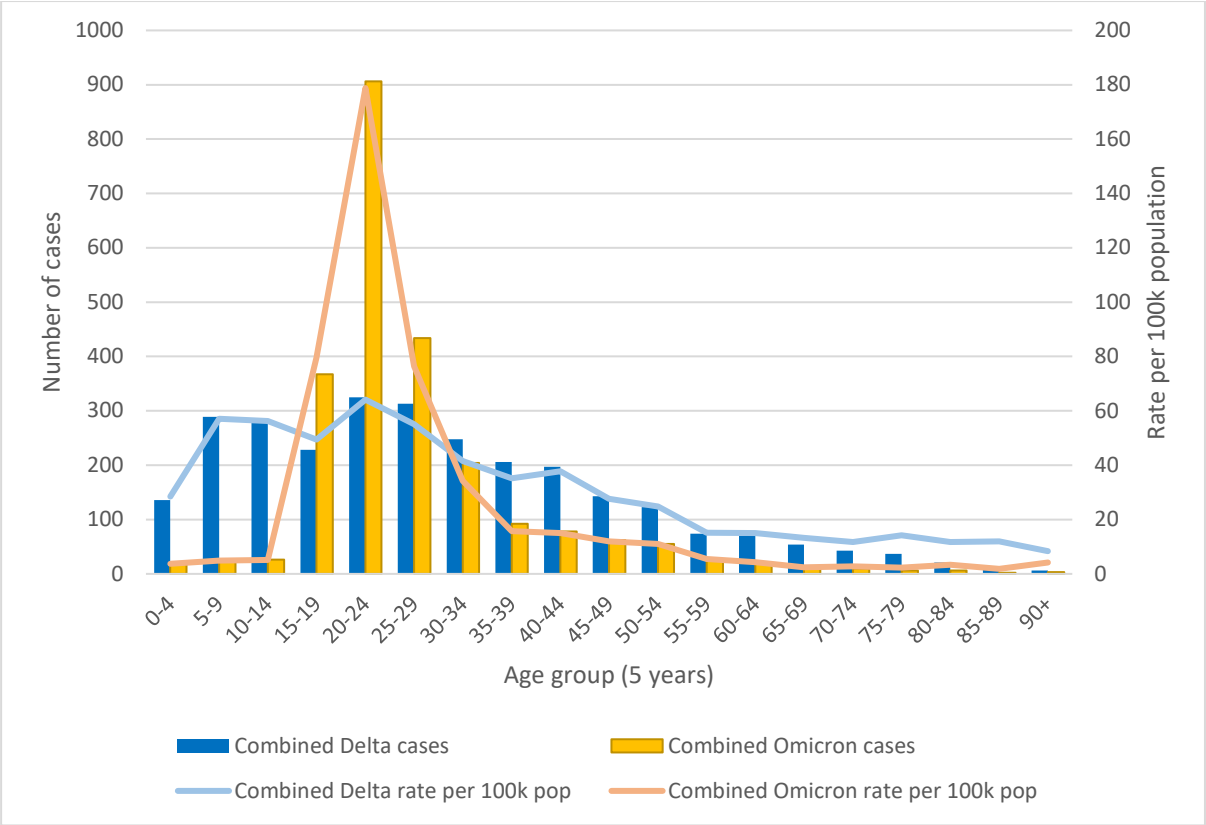

Table 1: Number and percentage of NSW COVID-19 cases with known variant, by variant from 27 November to 17 December 2021

| Variant | Number (%) |
|---|---|
| Confirmed Delta | 2,262 (43.8) |
| Probable Delta | 550 (10.7) |
| Confirmed Omicron | 818 (15.8) |
| Probable Omicron | 1,533 (29.7) |
| TOTAL | 5,163 (100) |

Overall, the cohort was 50.6% male and 48.9% female, with 0.5% of cases with data for sex missing (Table 2). The rate ratio of male to female cases was 1.10 in the Combined Delta group and 0.99 in the Combined Omicron group during the study period. The median age of the whole cohort was 24 years (IQR 19–36, range 0–102). The median age of the Combined Delta group was 27 (IQR 14–42) and the median age of the Omicron group was 23 (IQR 20–29). The age distribution of Omicron VOC cases differed greatly to Delta VOC cases, with age group-specific rates markedly lower in the 0–14 year age

groups before spiking in the in 15–29 year age groups, with the rate of Omicron VOC cases in the 20–24 year age group more than 2.5 times higher than the rate for Delta cases (Figure 2).

**Figure 2: Age distribution (total case numbers and rate per 100,000 population) of all NSW COVID-19 cases with known variant, by variant, from 27 November to 17 December 2021**




The majority of the total cohort had received two doses of an approved SARS-CoV-2 vaccine prior to their infection, however, the proportions of people two-dose vaccinated or zero-dose vaccinated (unvaccinated) varied greatly between the Delta VOC and Omicron VOC groups, with significantly more people who acquired Omicron VOC being two-dose vaccinated (49.6% in the Delta group vs 82.4% in the Omicron group) (Table 2). Forty-eight per cent of people who acquired Delta were unvaccinated, compared to 15% of people who acquired Omicron VOC.

Table 2: Demographic and vaccination characteristics of NSW COVID-19 cases by variant, from 27 November to 17 December 2021

| | Combined Delta n=2,812 | Combined Omicron n=2,351 | Total cohort n=5,163 | p-value^ |
|---|---|---|---|---|
| **Sex (%)** | | | | <0.001 |
| Female | 1,336 (47.5) | 1,187 (50.5) | 2,523 (48.9) | |
| Male | 1,451 (51.6) | 1,163 (49.5) | 2,614 (50.6) | |
| Not stated / missing | 25 (0.9) | 1 (0.0) | 26 (0.5) | |
| **Age group (%)** | | | | <0.001 |
| 0-4 yrs | 136 (4.8) | 18 (0.8) | 154 (3.0) | |
| 5-9 yrs | 289 (10.3) | 25 (1.1) | 314 (6.1) | |
| 10-14 yrs | 286 (10.2) | 26 (1.1) | 312 (6.0) | |
| 15-19 yrs | 228 (8.1) | 367 (15.6) | 595 (11.5) | |
| 20-24 yrs | 325 (11.6) | 906 (38.5) | 1,231 (23.8) | |
| 25-29 yrs | 313 (11.1) | 434 (18.5) | 747 (14.5) | |
| 30-34 yrs | 248 (8.8) | 204 (8.7) | 452 (8.8) | |
| 35-39 yrs | 206 (7.3) | 92 (3.9) | 298 (5.8) | |
| 40-44 yrs | 197 (7.0) | 78 (3.3) | 275 (5.3) | |
| 45-49 yrs | 143 (5.1) | 62 (2.6) | 205 (4.0) | |
| 50-54 yrs | 123 (4.4) | 55 (2.3) | 178 (3.4) | |
| 55-59 yrs | 74 (2.6) | 27 (1.1) | 101 (2.0) | |
| 60-64 yrs | 70 (2.5) | 20 (0.9) | 90 (1.7) | |
| 65-69 yrs | 54 (1.9) | 10 (0.4) | 64 (1.2) | |
| 70-74 yrs | 43 (1.5) | 10 (0.4) | 53 (1.0) | |
| 75+ yrs | 77 (2.7) | 17 (0.7) | 94 (1.8) | |
| **Aboriginal and/or Torres Strait Islander (%)** | | | | <0.001 |
| Yes | 108 (3.8) | 125 (5.3) | 233 (4.5) | |
| No | 2,602 (92.5) | 2,077 (88.3) | 4,679 (90.6) | |
| Missing | 102 (3.6) | 149 (6.3) | 251 (4.9) | |
| **Number of dose(s) of COVID-19 vaccine before infection (%)** | | | | <0.001 |
| Zero doses before infection | 1,343 (47.8) | 343 (14.6) | 1,686 (32.7) | |
| One dose before infection | 43 (1.5) | 12 (0.5) | 55 (1.1) | |
| Two doses before infection | 1,395 (49.6) | 1,938 (82.4) | 3,333 (64.6) | |
| Three doses before infection | 28 (1.0) | 55 (2.3) | 83 (1.6) | |
| Four doses before infection | 3 (0.1) | 3 (0.1) | 6 (0.1) | |

^ Chi-squared test comparison between Combined Delta cases and Combined Omicron cases. P values < 0.05 were considered statistically significant.

There were significant differences between the proportions of breakthrough infections in each group: 84.9% of Omicron VOC cases were breakthrough infections in fully vaccinated individuals, compared to 50.7% of Delta VOC cases. Disease severity outcome differences between the two groups were significant for hospitalisation due to COVID-19 (7.3% in the Delta group vs 3.4% in the Omicron group) and admission to an intensive care unit (ICU) or high dependency unit (HDU) (1.2% in the Delta group vs 0.1% in the Omicron group), and death due to COVID-19 (0.5% in the Delta group vs 0.1% in the Omicron group) (Table 3).

**Table 3: Breakthrough infection and disease severity outcome measures of NSW COVID-19 cases by variant, from 27 November to 17 December 2021**

| | Combined Delta n=2,812 | Combined Omicron n=2,351 | Total cohort n=5,163 | p-value^ |
|---|---|---|---|---|
| **Breakthrough infection in previously vaccinated (minimum 2 dose) individual (%)** | | | | <0.001 |
| Yes | 1,426 (50.7) | 1,996 (84.9) | 3,422 (66.3) | |
| No | 1,386 (49.3) | 355 (15.1) | 1,741 (33.7) | |
| **Case hospitalised due to COVID-19 (%)** | | | | <0.001 |
| Yes | 204 (7.3) | 81 (3.4) | 285 (5.5) | |
| No | 2,608 (92.7) | 2,270 (96.6) | 4,878 (94.5) | |
| **Case admitted to Intensive Care Unit/High Dependency Unit (%)** | | | | <0.001 |
| Yes | 35 (1.2) | 3 (0.1) | 38 (0.7) | |
| No | 2,777 (98.8) | 2,348 (99.9) | 5,125 (99.3) | |
| **Case died from COVID-19 (%)** | | | | 0.014 |
| Yes | 15 (0.5) | 3 (0.1) | 18 (0.3) | |
| No | 2,797 (99.5) | 2,348 (99.9) | 5,145 (99.7) | |

^ Chi-squared test comparison between Combined Delta cases and Combined Omicron cases. P values < 0.05 were considered statistically significant.

Cases were geographically clustered. The greatest proportion of total cases was recorded in the Hunter New England Local Health District (LHD) (Table 4). Hunter New England LHD also recorded the largest number of Omicron VOC cases, with 1,381 cases (58.7% of all Omicron cases), and the highest rate of Omicron VOC cases with 144 cases per 100,000 population in this period. The next highest rate of Omicron VOC cases was in Sydney LHD, with 25 cases per 100,000 population.

Table 4: NSW COVID-19 cases by Local Health District (LHD), breakdown by variant groups, from 27 November to 17 December 2021 (n=5,163).

| | Combined Delta (n=2,812) | | Combined Omicron (n=2,351) | | Total cases (n=5,163) |
|---|---|---|---|---|---|
| **Metro LHDs** | **Number of cases (%)** | **Rate per 100k pop** | **Number of cases (%)** | **Rate per 100k pop** | **Number (%)** |
| Nepean Blue Mountains | 66 (2.3) | 17 | 34 (1.4) | 9 | 100 (1.9) |
| Northern Sydney | 173 (6.2) | 19 | 85 (3.6) | 9 | 258 (5.0) |
| South Eastern Sydney | 443 (15.8) | 49 | 151 (6.4) | 17 | 594 (11.5) |
| South Western Sydney | 670 (23.8) | 63 | 193 (8.2) | 18 | 863 (16.7) |
| Sydney | 413 (14.7) | 63 | 166 (7.1) | 25 | 579 (11.2) |
| Western Sydney | 567 (20.2) | 54 | 227 (9.7) | 21 | 794 (15.4) |
| **Regional LHDs*** | | | | | |
| Central Coast | 74 (2.6) | 21 | 42 (1.8) | 12 | 116 (2.2) |
| Hunter New England | 85 (3.0) | 9 | 1381 (58.7) | 144 | 1466 (28.4) |
| Illawarra Shoalhaven | 81 (2.9) | 19 | 16 (0.7) | 4 | 97 (1.9) |
| Mid North Coast & Northern NSW | 140 (5.0) | 26 | 26 (1.1) | 5 | 166 (3.2) |
| Murrumbidgee & Southern NSW | 48 (1.7) | 10 | 9 (0.4) | 2 | 57 (1.1) |
| Far West & Western NSW | 47 (1.7) | 15 | 13 (0.6) | 4 | 60 (1.2) |
| **Unknown** | 5 (0.2) | | 8 (0.3) | | 13 (0.3) |

*Some regional LHDs have been combined due to small numbers: Far West with Western NSW, Mid North Coast with Northern NSW, Murrumbidgee with Southern NSW.

Case notifications began increasing steadily from 7 December 2021, with steep increases seen from 13 December 2021 to the end of the study period on 17 December 2021 (Figure 3). Looking at only cases with known variant, high numbers of Omicron VOC cases are responsible for the spike in cases as the outbreak accelerates (Figure 4). Omicron VOC had replaced Delta VOC as the dominant circulating SARS-CoV-2 variant in NSW by 13 December 2021, 15 days after the first Omicron VOC case had been detected (Figure 5).

Figure 3: Epidemic curve of all NSW COVID-19 cases by notification date from 27 November to 17 December 2021 (n=13,901).

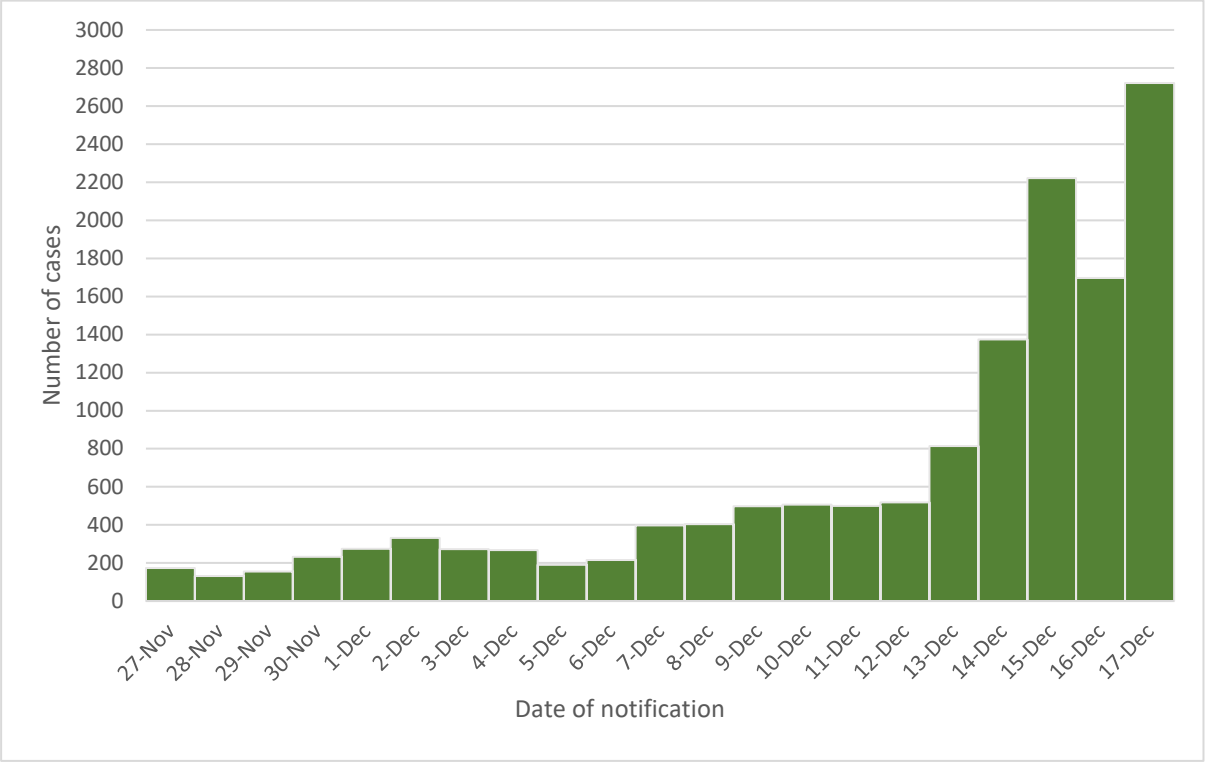



Figure 4: Epidemic curve of all NSW COVID-19 cases with known variant, by notification date, breakdown by variant, from 27 November to 17 December 2021 (n=5,163)

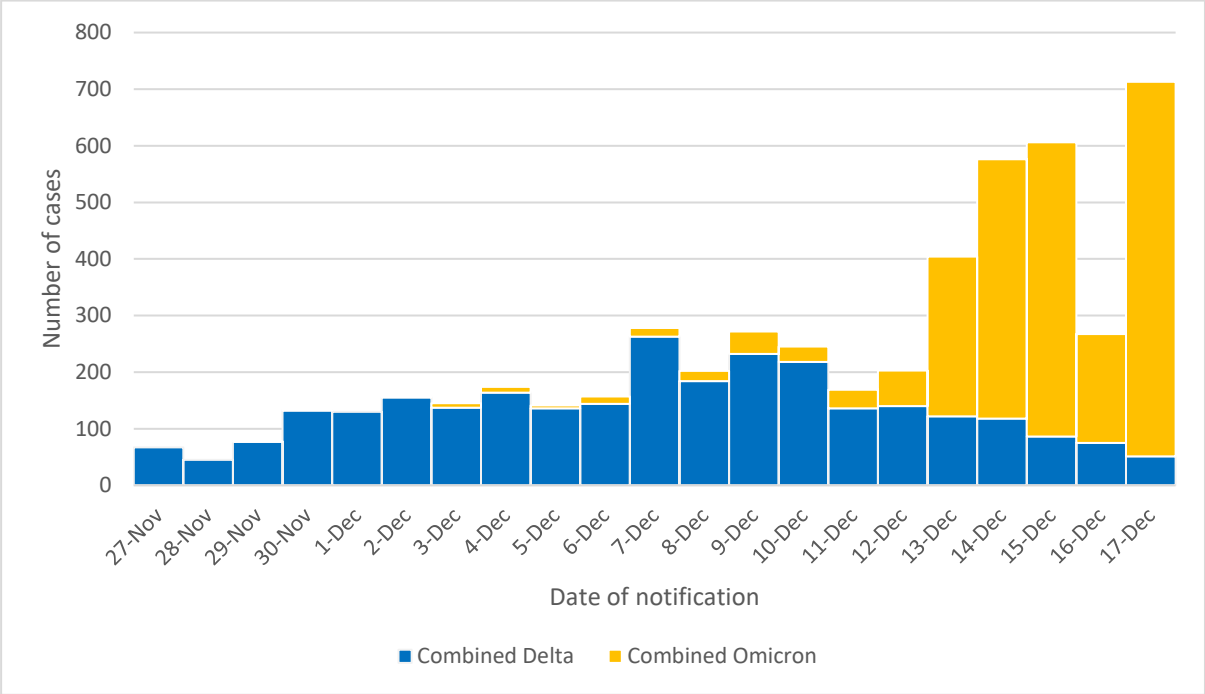
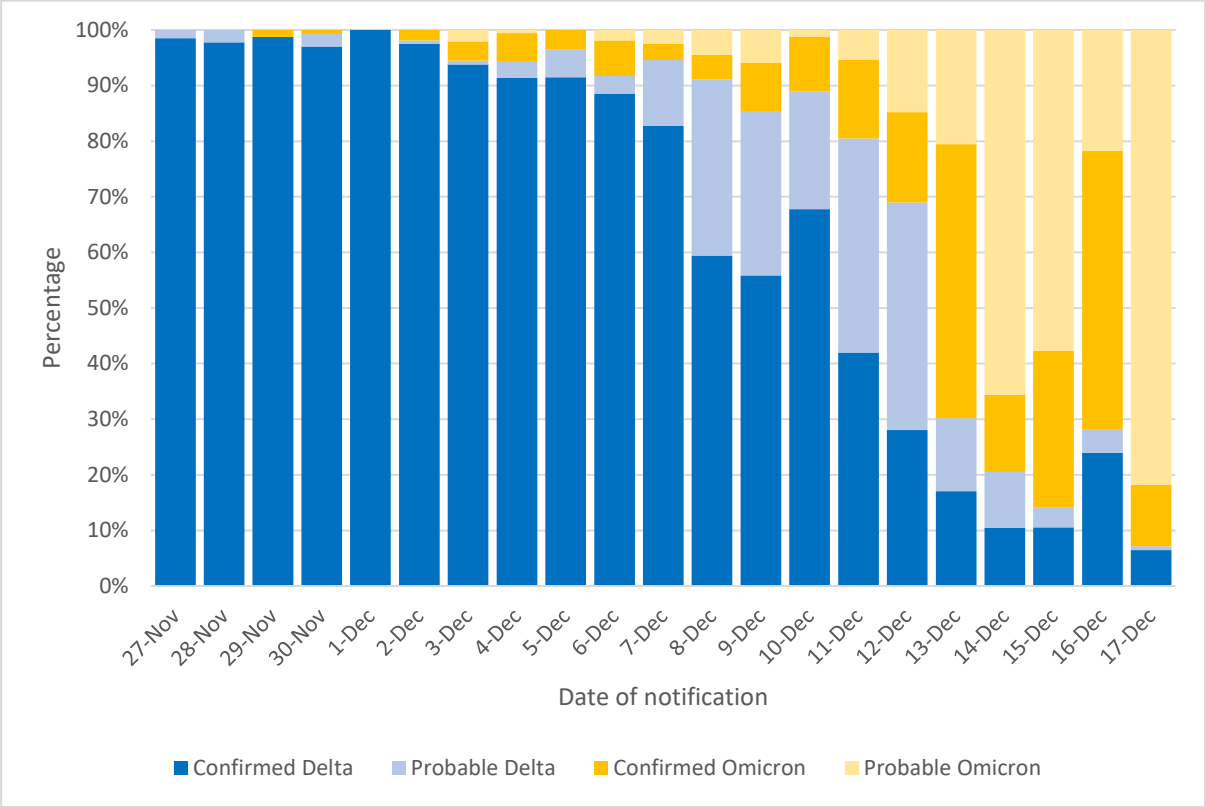


Figure 5: Percentage circulating variant, NSW COVID-19 cases with known variant, by notification date, from 27 November to 17 December 2021




## Discussion

The distinctly younger age profile of the Combined Omicron group, together with the geographic spread of cases concentrated in the Hunter New England LHD, largely reflects the setting of two major transmission events in Newcastle, a large regional city to the north of Sydney.[11] Two people who had attended a boat party in Sydney where Omicron VOC cases had been detected left their isolation to attend a party at a nightclub in Newcastle on 8 December 2021. Two days later, on 10 December 2021, at least one person from the nightclub party attended a university graduation ball, also in Newcastle. A research study in preprint that has examined vaccine effectiveness against Omicron VOC in these two 'super-spreader' events reports 397 SARS-CoV-2 cases arising from these two events alone.[12] Among attendees with a PCR test result recorded at 12 days after exposure, 55.1% (295/535) from the nightclub party and 54.0% (102/189) from the graduation ball were SARS-CoV-2 positive.[12] Both events would have acted as significant amplifying events, seeding many further chains of transmission in the Newcastle area and beyond.

The notable rates of breakthrough infections in fully vaccinated (minimum two dose, greater than 14 days prior to infection) individuals among the Omicron VOC cases, compared to the Delta VOC cases,

highlights the concerns around effectiveness of the widely used vaccines at the time. Vaccine effectiveness (VE) studies in Australia and internationally have reported higher rates of breakthrough infections with Omicron VOC than Delta VOC.[13-15]

The wave of infections caused by the Delta VOC outbreak that began in NSW in June 2021 was subsiding by October 2021, and many lockdown period restrictions were lifted, culminating in the removal of compulsory hotel quarantine for incoming travellers on 1 November 2021.[16] The Delta VOC outbreak had spurred high rates of vaccination across Australia in 2021. By the end of November, as Omicron VOC arrived, NSW had the second highest two-dose vaccinated population in Australia, after ACT, with 92.5% of the population having received at least two doses.[17] Vaccination was offered in stages based on age groups, with younger groups able to access vaccination later than older age groups. There were also differences in the vaccines used for different age groups, with older age groups offered the AstraZeneca ChAdOx1 nCoV-19 vaccine and younger age groups restricted to accessing only the Pfizer-BioNTech BNT162b2 vaccine.

Nationally, at the end of November 2021 75.7% of people aged 20–24 and 78.1% of people aged 25–29 were two-dose vaccinated.[17] While these are lower levels of vaccination than in older age groups, people in younger age groups were, on the whole, more recently vaccinated than older age groups due to the staged eligibility of COVID-19 vaccination, which would have conferred greater protection than for those with a longer time since vaccination. A VE study conducted in Australia in this period reported waning immunity against infection following a booster dose as time since vaccination increases, falling from 70.7% when the booster dose was administered 5–29 days before testing to 13.5% when the booster dose was administered greater than 120 days before testing.[18] However, the Omicron VOC group, overall younger than the Delta VOC group and therefore likely more recently vaccinated, showed a higher proportion of breakthrough infections.

A large VE study in England found no effect against Omicron VOC infection from 20 weeks after two AstraZeneca ChAdOx1 nCoV-19 doses, but VE of 65.5% between 2 to 4 weeks after two Pfizer-BioNTech BNT162b2 doses, falling to 8.8% at 25 or more weeks.[19] If differences in vaccine type were a factor for breakthrough Omicron VOC infections, then one might have expected to see higher numbers of older age groups in the Omicron VOC group, as these people would be more likely vaccinated with the AstraZeneca vaccine, thought to be less effective against Omicron VOC infection, and more likely vaccinated earlier, thus with a longer time since vaccination. We did not observe such a difference in this cohort.

The Omicron VOC cases in our cohort were more likely to be vaccinated than the Delta VOC cases, which we can interpret in the context of evidence about diminished protection against Omicron VOC

infection from vaccination as expected higher rates of breakthrough infections. However, another identified benefit of vaccination against SARS-CoV-2 is the protection offered against severe disease. We did observe fewer severe disease outcomes in the Omicron VOC group compared to the Delta VOC group. Protection conferred from vaccination may be a factor in this result, rather than differences in virulence of the different variants. A study examining severe disease outcomes in vaccinated SARS-CoV-2 Omicron VOC cases in Spain in early 2022 found that vaccination greatly reduced the risk of hospitalisation and severe outcomes (ICU admission and/or death).[20] The higher rates of severe outcomes in the Delta VOC group may relate to their overall lower levels of vaccination.

## Limitations

The Delta VOC and Omicron VOC groups had different exposure profiles during the study period. A majority of Omicron VOC cases resulted from large known clusters in nightclubs and schools thus, as expected, the Omicron group had a higher proportion of cases in younger age groups and showed distinct geographical clustering. This has limited our ability to draw conclusions about the different epidemiological profiles of the two variant groups using descriptive statistics. It has also impacted our ability to draw conclusions about differential disease severity outcomes. The younger age profile of the Omicron group would put this group at lower risk of hospitalisation and/or death, and so we cannot say to what degree observed differences in disease severity between the two groups relate to the average age and general health of the group or to the relative severity of the illness.

A multivariate analysis with more variables, including time since vaccination, any prior SARS-CoV-2 infections and past medical history of chronic diseases, together with more case observations in both groups would be required to investigate this more thoroughly. Descriptive analyses are not sufficient to draw conclusions about causality or risk.

*Changes in disease control guidelines & surveillance during the study period*

The rules and guidelines around COVID-19 response were evolving rapidly in this period. The Communicable Diseases Network Australia (CDNA) Series of National Guidelines (SoNG) was revised during the study period, on 9 December 2021, to reflect emergence of the Omicron VOC, with updated content on the disease, the case definition, genomic sequencing, release from isolation criteria, close contact definition, management of contacts, and use of vaccination in outbreak situations. These changes may have impacted the way that cases were identified, counted and followed up.

*Ascertainment biases*

The Probable Omicron group is identified by an S gene dropout/S gene target failure in the PCR test. The PCR test platform capable of detecting an S gene dropout was the ThermoFisher TaqPath assay used only by Histopath laboratories. The detection of this group will be influenced by the volume and distribution of specimens tested using this particular PCR assay and platform.

Similarly, specimens which underwent WGS at the NSW reference laboratory, ICPMR, had a different profile to those that did not. As case numbers escalated during the Delta VOC outbreak, NSW shifted from a strategy of conducting WGS on all viable specimens to a selective sampling strategy focused on specimens from cases involved in outbreaks in institutions, cases who had acquired their infection overseas, and cases that were seriously ill in ICU/HDU. The WGS strategy accommodated ad hoc requests for sequencing, for example in high-risk settings such as residential aged care facilities where outbreak investigations focused on understanding if the outbreak had been caused by one or more introductions, as a test of infection prevention and control protocols.

We believe that the proportion and distribution of Probable Omicron cases, identified using the ThermoFisher TaqPath assay operated by Histopath laboratories, is more representative of the true proportion and distribution of Omicron VOC cases in the population. Cases undergoing WGS and subsequently identified as Confirmed Omicron underwent targeted selection in an attempt to respond to specific public health inquiries and data requests.

*Impact of vaccination*

Vaccination endpoints are subject to matching errors between NCIMS and AIR. We were also unable to look at time since last vaccination in detail as this was out of scope for this analysis. Waning immunity from vaccination may have played a role in both the number of infections and the severity of disease experienced.

*Non-pharmaceutical and behavioural interventions*

Any differences in non-pharmaceutical interventions (masks, density restrictions in venues) where exposure occurred may bias results.

*Outcome definitions*

Hospitalisation endpoint may be affected by lack of a clear case definition for a COVID hospitalisation in the Patient Flow Portal (PFP). Emergency Department visits may be classified as admissions by the PFP. Some hospitalisations and ICU admissions may be unrelated to SARS-CoV-2 infection.

## Conclusions

In little over two weeks following its introduction into the NSW population, Omicron VOC had replaced Delta VOC as the predominant circulating SARS-CoV-2 variant in NSW. Omicron VOC cases drove a spike in case notifications, triggering the largest wave of COVID-19 cases in NSW at the time, and changing the landscape of the outbreak. We observed fewer severe disease outcomes (hospitalisations, ICU/HDU admissions, deaths due to COVID-19) in cases infected with Omicron VOC than in cases infected with Delta VOC. In a highly vaccinated population like NSW, Omicron VOC caused a higher proportion of breakthrough infections (infections in people vaccinated with at least two doses more than 14 days prior to infection) than Delta VOC.

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# CHAPTER 6

## Teaching applied epidemiology

## Chapter 6: Table of contents

## List of abbreviations

| | |
|---|---|
| AMR | Antimicrobial resistance |
| AURA | Antimicrobial Use and Resistance in Australia |
| CARAlert | National Alert System for Critical Antimicrobial Resistances |
| CPE | Carbapenamese-producing *Enterobacteriales* |
| DND*i* | Drugs for Neglected Diseases initiative |
| HAT | Human African Trypanosomiasis |
| LFF | Lessons from the Field |
| MRO | Multidrug resistant organisms |
| NTD | Neglected tropical diseases |
| POC-CCA | Point-of-care Circulating cathodic antigen |
| STH | Soil-transmitted helminths |
| TTFY | Teaching to First Year scholars |

## Introduction

There are two teaching requirements in the MAE Program that scholars must complete to meet the competency of teaching field epidemiology: teaching to first year scholars and presenting a lesson from the field to their cohort. This chapter describes those teaching activities.

## Teaching to First Year Scholars

Our whole cohort discussed session topic ideas together and then split into four groups, aligned with our preferred topics and areas of expertise, to run the full day of teaching to first years on Friday 11 March 2022. I joined the group presenting on antimicrobial resistance (AMR) and genomics. I presented the work I had done on multidrug resistant organism (MRO) surveillance in NSW. We chose this topic because AMR is one of the greatest challenges we are facing in health and, with the increase in attention on AMR, all field epidemiologists should have a basic level of familiarity with the topic.

### Structure of the session

The title of our session was, "Forget Covid: Why you should be afraid of AMR and what to do about it." We divided the session into five sections and each presenter took one section. The sections were:

1. AMR in public health – What is AMR and why should epidemiologists care about it
2. AMR/MRO surveillance – How do we conduct surveillance for AMR in Australia?
3. AMR and genomics – A crash course in the microbiology of AMR
4. Case study: CPE surveillance in South Australia – Detecting CPE outbreaks
5. Case study: Epidemiology in Victoria – A world-leading study combining genomics and epidemiology

The overall learning objective for the session was for the first-year scholars to be able to describe why AMR is a public health issue and describe the components of the AMR surveillance system in Australia, using Carbapenamese-producing *Enterobacteriales* (CPE) as an example.

My section was structured as follows:

- How do we conduct surveillance for AMR?
- What are Multidrug resistant organisms?
- What is CPE? Breaking it down
- How does MRO surveillance work in NSW?
    - What is notifiable?
    - When do specimens get collected?

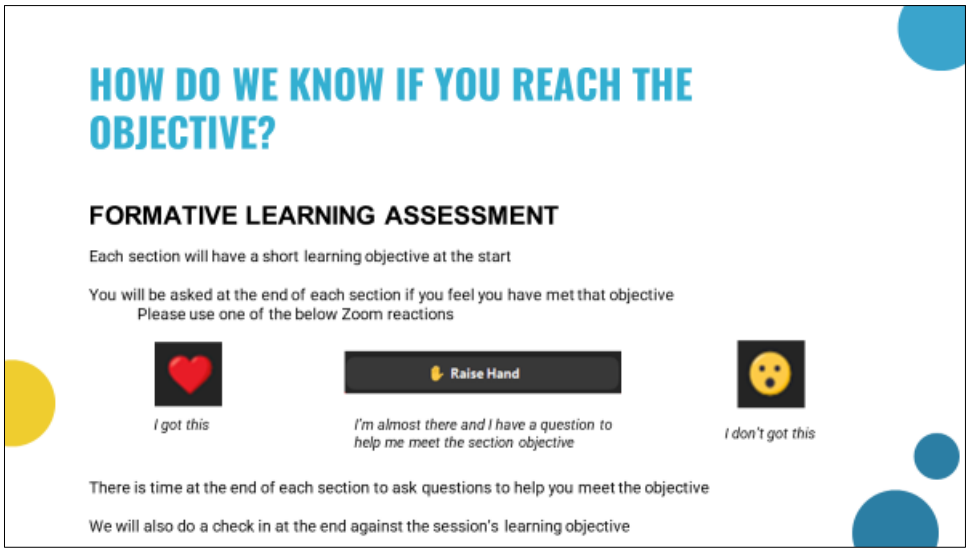
    - Colonisation vs infection
    - Challenges for surveillance for MROs
- MRO surveillance in other jurisdictions
- National surveillance – Antimicrobial Use and Resistance in Australia (AURA) Surveillance System and National Alert System for Critical Antimicrobial Resistances (CARAlert)
- Public health actions arising from MRO surveillance

The learning objectives for my section were for the first year scholars to understand some of the different ways in which surveillance for AMR operates in Australia, and identify some of the issues and challenges with surveillance for AMR. A copy of the presentation slides is contained in Appendix A.

### Pedagogy

We used formative learning assessments for the session, which involved setting learning objectives for each section of the session and using the 'react emojis' in Zoom to check in with the audience in each section to confirm their understanding of the content, ask their opinion about whether the learning objective has been met, and allow frequent opportunities for participants to ask questions and seek clarification (Figure 1). This method worked well for our audience and allowed us to keep track of engagement.

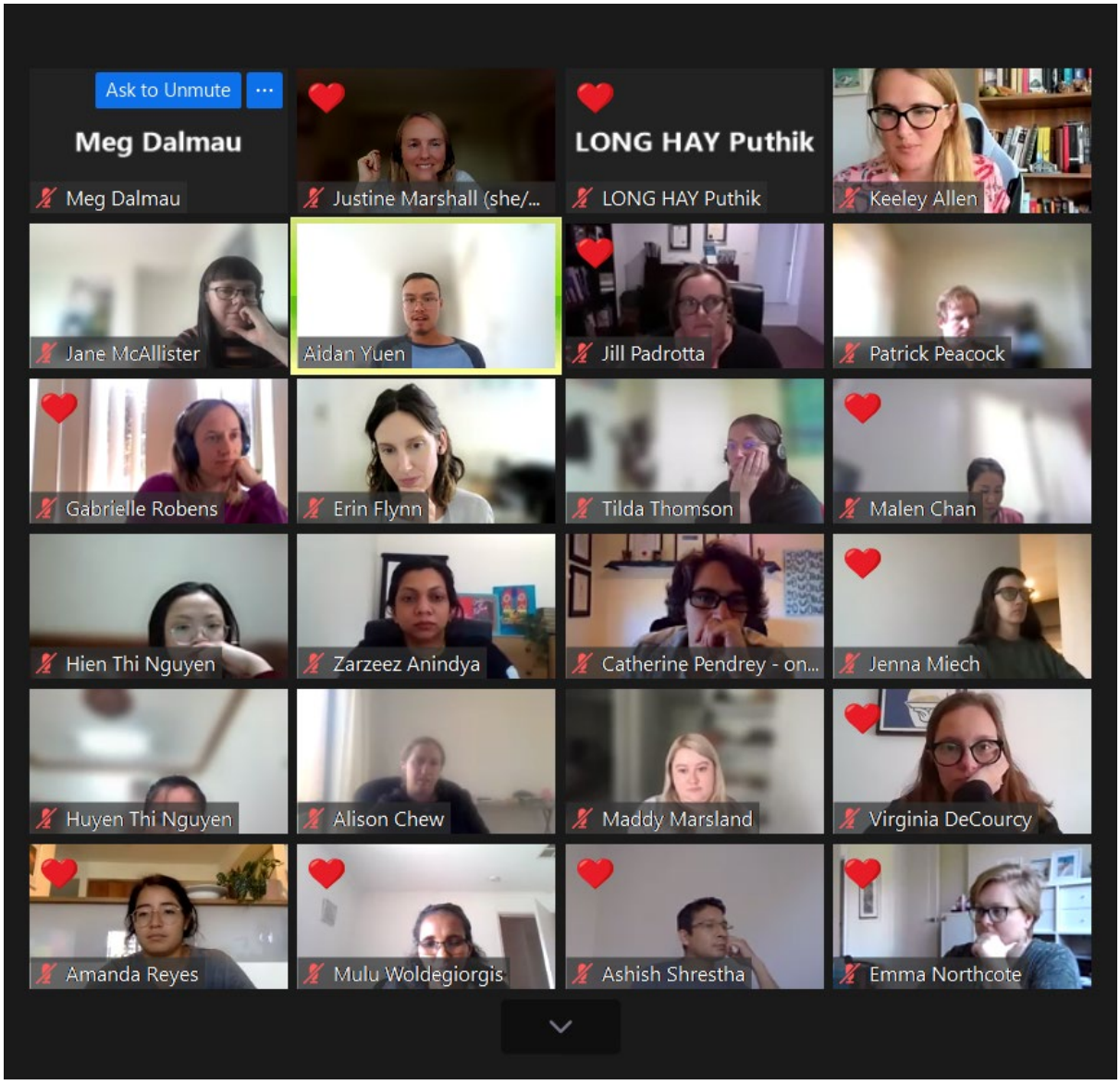
**Figure 1: The formative learning assessment method used in the Teaching to First Year Scholars session**




A heart emoji indicated that the participant understood all elements of the section content. A raised hand indicated that the participant had a question about an element of the section content. Questions were asked and answered live in the session. A shocked face emoji indicated that a participant did not

understand the section. It was not compulsory to register an emoji response and some participants did abstain from answering in some sections. Figure 2 is a screenshot showing an emoji check-in in action.

Figure 2: Screenshot of an emoji check-in at the end of one of the sections during our Teaching to First Years session on 11 March 2022



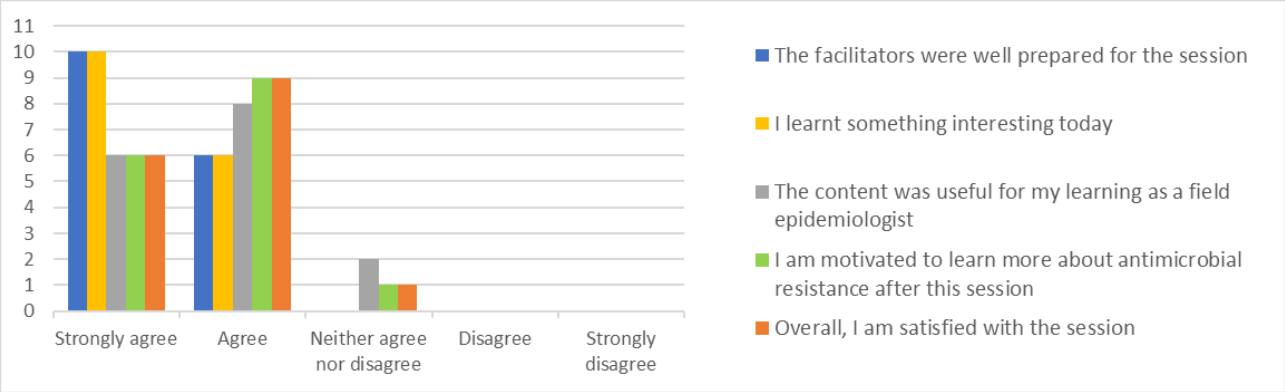

We used other tools to make the session interactive, including a brainstorm poll, a word guessing game based on the popular "Wordle" game, and a quiz.

## Evaluation

We distributed an evaluation survey at the end of the session, which received 16 responses. The survey feedback was positive, with no respondents disagreeing with any of the evaluation statements.

Overall satisfaction with the session was 94% (15/16). Figure 3 shows the distribution of responses to the evaluation questions.

**Figure 3: Evaluation question responses from participants in the Teaching to First Years session on 11 March 2022 (n=16)**




As a group we were happy with how the session went. All presenters put a lot of effort into their sections. We met online to discuss and develop the content, reviewed each other's slides, and had a practice run together before the final presentation. It is difficult to present content that increases in complexity within a session, and keep the audience engaged to the end, and the evaluation survey showed that we had reasonable success at this.

## Lessons from the Field

The Lessons from the Field (LFF) component is intended to create opportunities for peer-to-peer teaching and learning, based on real world challenges. Our cohort divided itself into two groups alphabetically by first name. My group scheduled our LFFs over a series of Wednesday mornings between May and September, with the sessions held on Microsoft Teams. I presented my LFF on 21 September 2022 to my group.

### Structure of the session

I presented a session on neglected tropical diseases (NTDs), with a focus on diagnostics choices and control strategies. I chose this topic after consultation with my group and my academic supervisor. I wanted to tap into my previous work experiences on soil-transmitted helminth and schistosomiasis research projects in Ethiopia to share a perspective on a different 'field.' I also wanted to look at operational research and international contexts, acknowledging that many in my cohort are interested in work in international settings.

The learning objectives for my session were to:

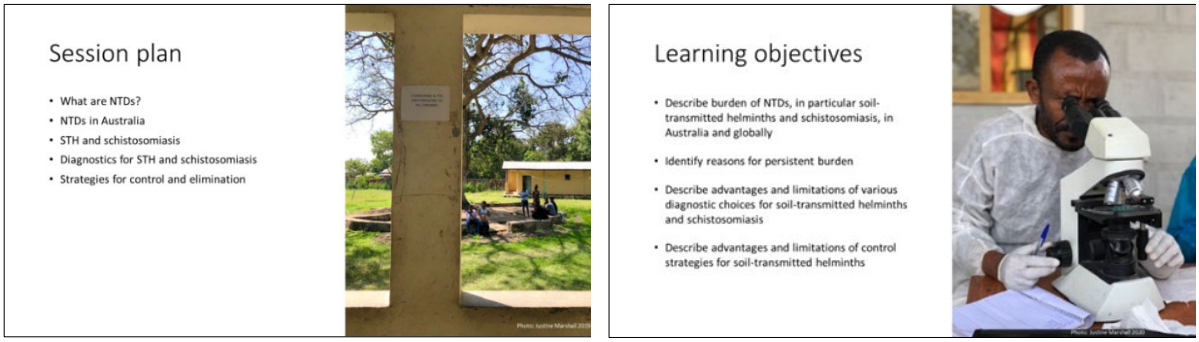
- Describe burden of NTDs, in particular soil-transmitted helminths and schistosomiasis, in Australia and globally
- Identify reasons for persistent burden
- Explain advantages and limitations of various diagnostic choices for soil-transmitted helminths and schistosomiasis
- Discuss advantages and limitations of control strategies for soil-transmitted helminths

In preparation for the session, I asked participants to watch a short video by the Drugs for Neglected Diseases initiative (DND*i*) about the development of a new medicine to treat Human African Trypanosomiasis (HAT), or sleeping sickness, which is caused by infection with the protozoan parasites *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, transmitted by the bite of the tsetse fly (*Glossina* genus).

The film, called "A Doctor's Dream: A pill for sleeping sickness," shows the discovery, development, and clinical trials of fexinidazole, the first all-oral drug that can treat both stages of HAT. The film allowed participants to learn about HAT, and also gave an introduction to the reality of conducting research on neglected tropical diseases in some difficult environments. The trials took place in the Central African Republic and the Democratic Republic of the Congo, where operational challenges included remote locations of cases, inaccessible terrain, lack of infrastructure and laboratory equipment, and political instability. A collection of partners, led by DND*i*, successfully carried out the trials and fexinidazole was approved for use in November 2018.

During the session I presented an overview of NTDs, diagnostics methods, and control strategies, and had a guided discussion with the group about the application of diagnostics and control strategies in different scenarios, including low and high prevalence settings, and research or surveillance settings. Figure 4 shows the slides outlining the session plan and learning objectives for the audience.

**Figure 4: The session plan and learning objectives of the LFF session on NTDs**



The outline of the session was:

- What are Neglected Tropical Diseases?
    - Overview
    - NTD quiz
    - Lifecycles of parasites, including One Health element of NTDs (animal, environment and climate influences)
- NTDs in Australia
    - Trachoma
    - *Strongyloides stercoralis*
- Soil-transmitted helminths and schistosomiasis
- Diagnostics for STH and schistosomiasis – overview and applications
    - Kato Katz
    - Point of care Circulating cathodic antigen (POC-CCA)
    - qPCR
    - Sensitivity and specificity
- Strategies for control and elimination of STH and schistosomiasis
    - Mass drug administration
    - Water, sanitation and hygiene
- Choices based on scenario: research or surveillance?
- Test your knowledge quiz

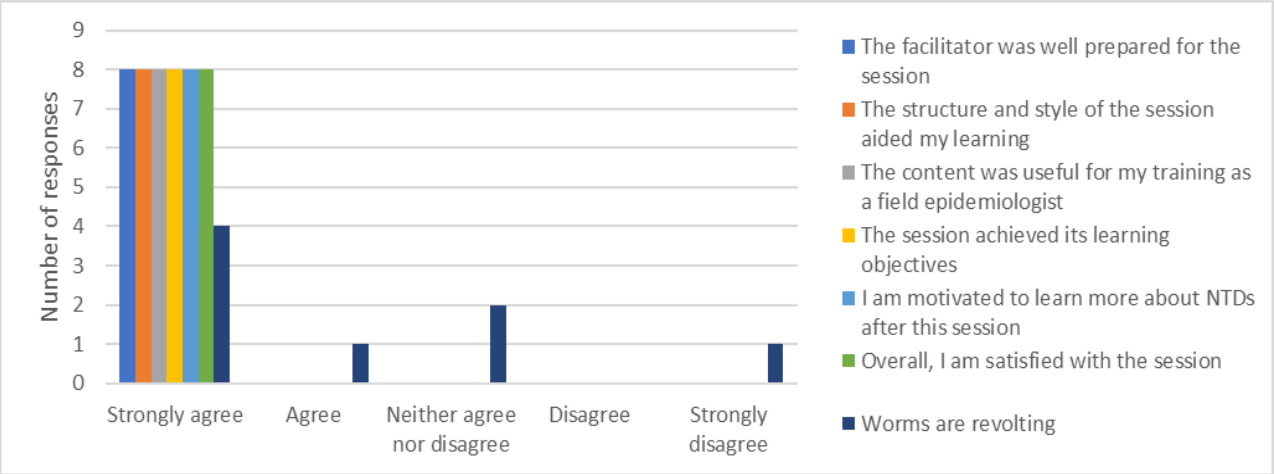
I made the session interactive, with a quiz on NTDs and discussion points along the presentation, and engaged the audience in the realities of research in low-resource settings with photos from the field.

A copy of the presentation slides is contained in Appendix B.

## Evaluation

I distributed an evaluation survey at the end of the session, which received eight responses. Participants reported finding the session enjoyable and valuable for their field epidemiology training, with all eight respondents indicating strong agreement with six of the seven evaluation questions. Responses to the final question were mixed, a likely reflection of various factors including social conditioning, philosophical attitudes towards nature, and personal ick thresholds. Figure 5 shows the distribution of the responses to the evaluation questions.

Figure 5: Evaluation question responses from participants in the LFF session on 21 September 2022 (n=8)

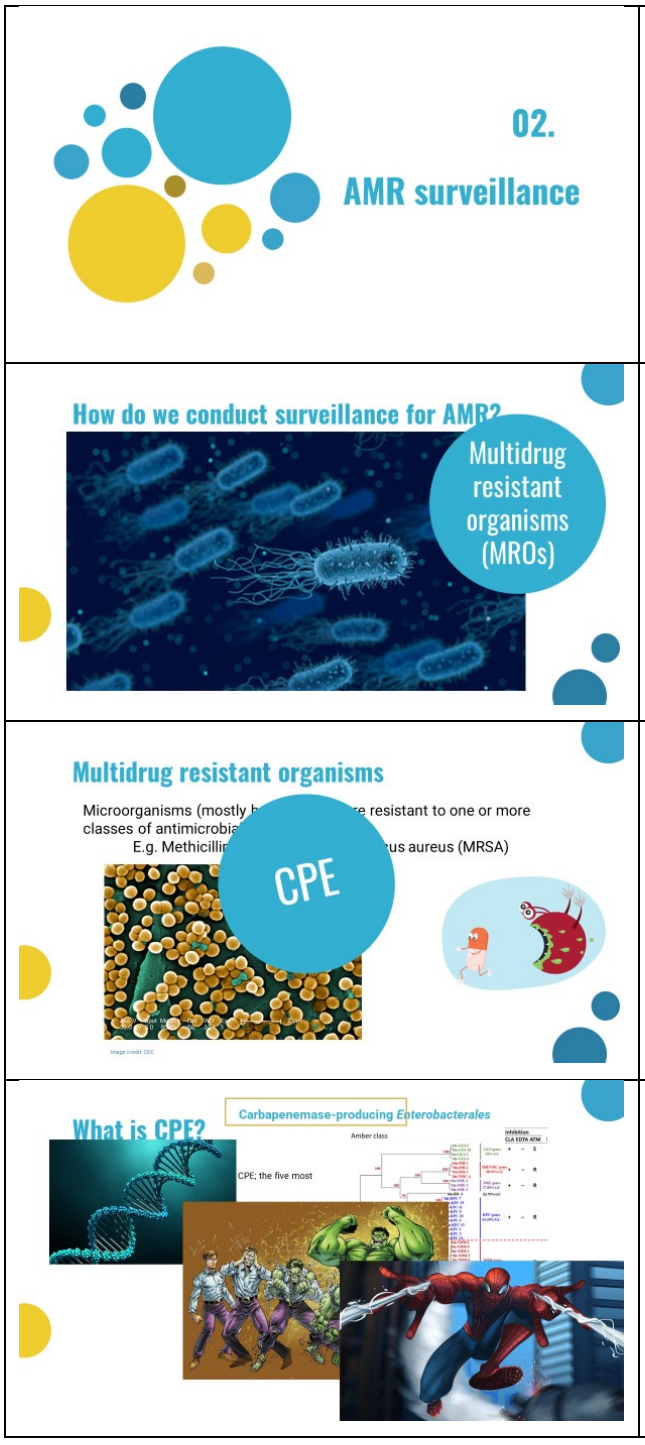



I thought the session went well, although it ran slightly longer than intended and I should have had a timed practice run before presenting. Overall, I enjoyed presenting on this topic to my peers, and was pleased to be able to share some of my fieldwork experiences with them.

## Conclusion

The teaching activities I participated in as part of this competency have served to confirm my enjoyment of teaching, training, and adult learning. The collaborative and thoughtful discussions that come about when you bring together people with diverse lived and professional experiences enrich all participants, including those in the 'trainer' role. It is a satisfying experience to share knowledge and to grow together.

## APPENDIX A: Presentation slides from Teaching to First Year Scholars session, 11 March 2022



## How does it work in NSW?

## What is notifiable in NSW?

**Carbapenemase-producing *Enterobacterales* (CPE) infection or colonisation – since Feb 2019**
Case definition in NSW
Confirmed CPE Case: A person with a species of *Enterobacterales* isolated from routine clinical or screening specimens (infection or colonisation) where a carbapenemase gene is detected in a sample or isolate irrespective of phenotypic susceptibility.

***Candida auris* infection and colonisation – since June 2020**

**In NSW:**
- We count the organism, not the gene
- We don't collect any enhanced surveillance info – travel history, previous hospitalisation
- We don't know if a notification is a colonisation or an infection
- Can be colonised for years

## When do specimens get collected?

Screening varies between facilities

What is the problem with this?

Which criteria/settings trigger testing?
Are these uniform?
Agreed statewide set of 'moments for testing'?
Are these suitable(clinical/surveillance)?
Who could we be missing?

## Colonisation vs infection

**Specimens from NON-STERILE sites, e.g. faeces**

In most cases, people carry CPE in their gut without it causing any symptoms or an infection. This is known as colonisation.

If you have CPE, extra precautions will need to be taken on admission to a health care or residential care facility to prevent CPE spreading to other people

**Specimens from normally sterile sites, e.g. blood**

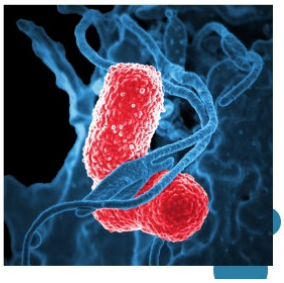
What do we do with the knowledge that there are 100 colonized people? Or 100 infections? Are these different, or can we lump them together ?

## Challenges of surveillance for MROs

The shift from health care facility to statewide

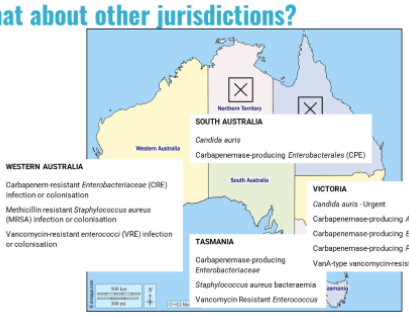
Shame, stigma and secrecy!

Without combining epi and genomics, you can't solve the problem



## What about other jurisdictions?

## What about other jurisdictions?




## AURA & CARAlerts

www.safetyandquality.gov.au


**Antimicrobial Use and Resistance in Australia (AURA) Surveillance System**
provides data and information to support Australia's strategic response to AMR

Established in 2014

The AURA Surveillance System collects data from hospital and community settings to provide a comprehensive national and regional picture of antimicrobial usage and AMR.

CAR Alerts – reporting on high priority MROs

**Voluntary, national surveillance**

## Public health actions arising from MRO surveillance

What are we trying to achieve?

- Estimate scope and magnitude of MROs
- Review the geographic and demographic distribution
- Detect outbreaks
- Evaluate control measures
- Program monitoring
- Health system monitoring for resource allocation
- Policy analysis
- Generate hypothesis and stimulate applied research


Tracking MROs across facilities – we know that transmission occurs in different facilities, if we want to break transmission chains we need to have that higher view – and we need to combine the epi and the genomics…

**How do we do that?**

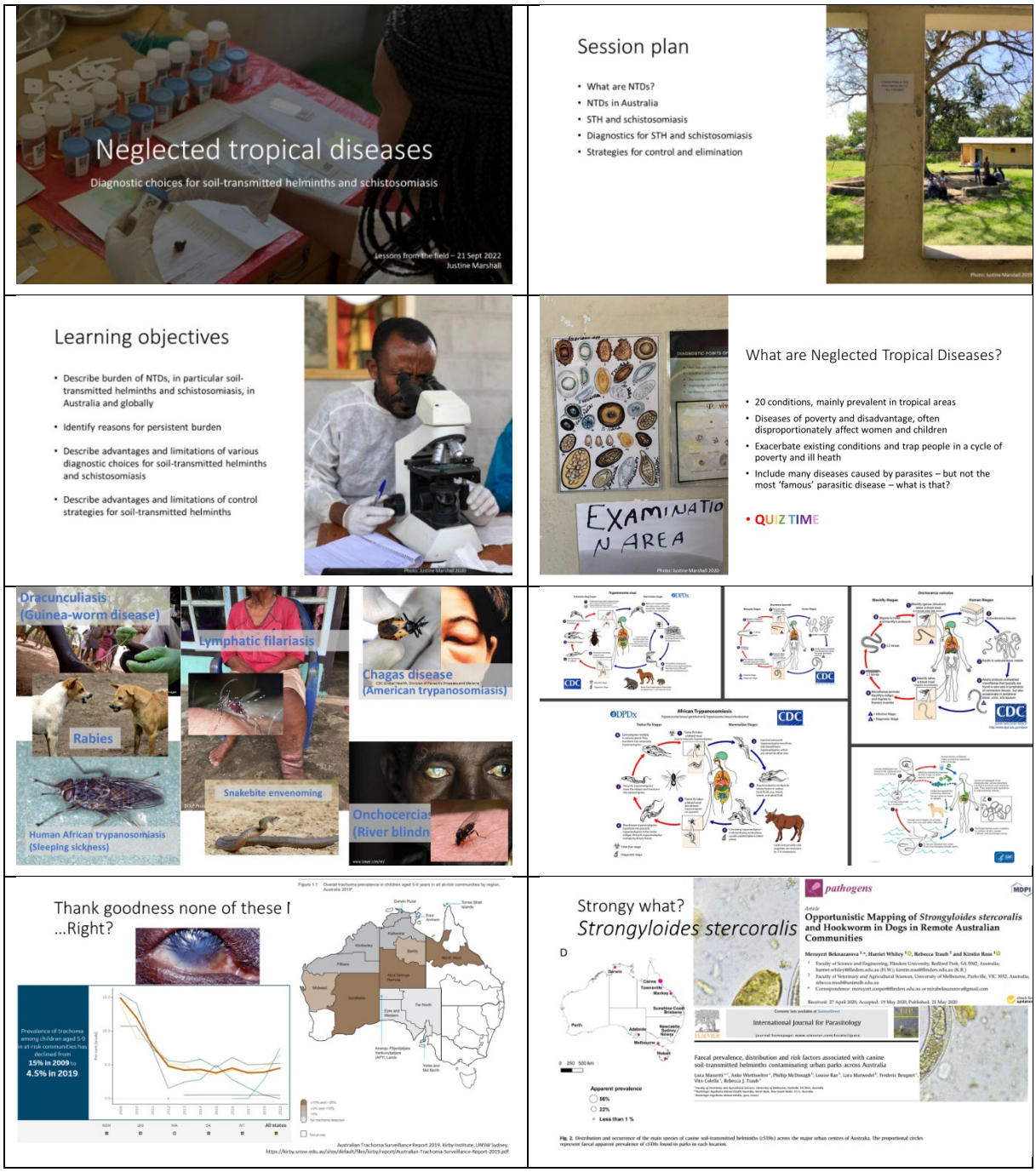
## CHECK IN!

## SECTION OBJECTIVE

By the end of this section, scholars will be able to:
- Understand some of the different ways in which surveillance for AMR operates in Australia
- Identify some of the issues and challenges with surveillance for AMR

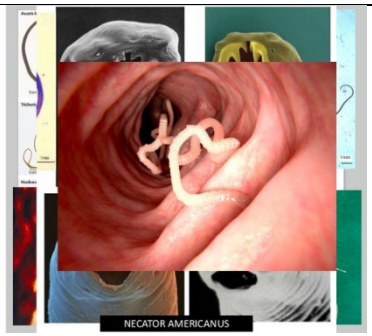
Raise Hand

## APPENDIX B: Presentation slides from Lesson from the Field session, 21 September 2022



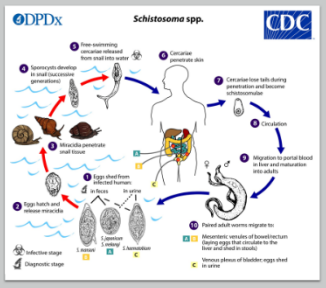
## Soil-transmitted helminths

- Found worldwide, 1.5 billion people infected
- Collection of species, including:
  - *Ascaris lumbricoides* (roundworm)
  - *Trichuris trichiura* (whipworm)
  - *Necator americanus* and *Ancylostoma duodenale* (hookworms)
- Life cycle stages in the human body, stages in the soil
- Transmission via fecal-oral route (but hookworms burrow into your feet)
- Heavy infection can cause a range of health problems, including abdominal pain, diarrhoea, blood and protein loss, rectal prolapse, and physical and cognitive growth delay
- Treated with Albendazole




## Schistosomiasis

- Blood trematodes (flukes) in the genus *Schistosoma*. (aka Bilharzia)
- Different species, different geography
- More than 200 million people infected worldwide
- Can be either gastrointestinal schisto or genito-urinary schisto, depending on species
- Reservoirs: cattle, dogs, cats, rodents, pigs, horses, and goats
- Intermediate hosts: snails of the genera Biomphalaria, (*S. mansoni*), Oncomelania (*S. japonicum*), Bulinus (*S. haematobium*).
- Symptoms: abdo pain, enlarged liver, problems passing urine
- Treated with Praziquantel




## Diagnostics

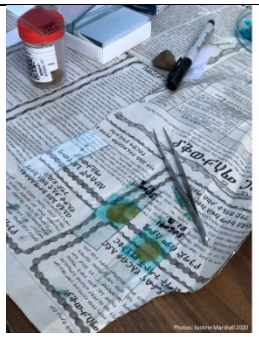
- Kato Katz – thick smear copromicroscopy
- Point of Care Circulating Cathodic Antigen (POC-CCA) – a urine test
- (Quantitative) Polymerase Chain Reaction – (q)PCR

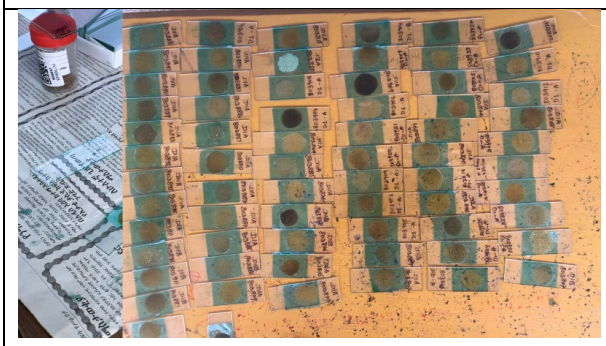
## Kato Katz

- Examine stool under microscope to identify helminth eggs and certain *Schistosoma* species eggs
- Pros – low tech, cheap, can be performed anywhere
- Cons – requires skilled microscopists and quality of test relies on quality of reading, hookworm eggs disintegrate quickly so slides need to be read within 30-60 min of prep, eggs clump together and can be missed



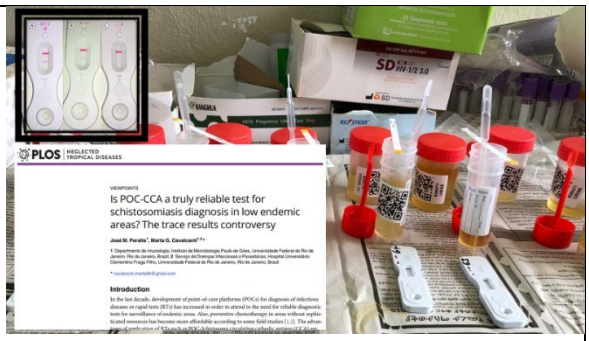




## POC-CCA

- Point of care (POC) Circulating cathodic antigen (CCA)
- Used for *Schistosoma mansoni* – intestinal schistosomiasis (can also detect medium to high level *S. haematobium* ?)
- Detects *Schistosoma* circulating antigens from adult worms that are ultimately secreted into urine
- Pros – quick (20 minutes), urine easier to collect, low tech, can be performed anywhere
- Cons – confusion over interpretation of trace results



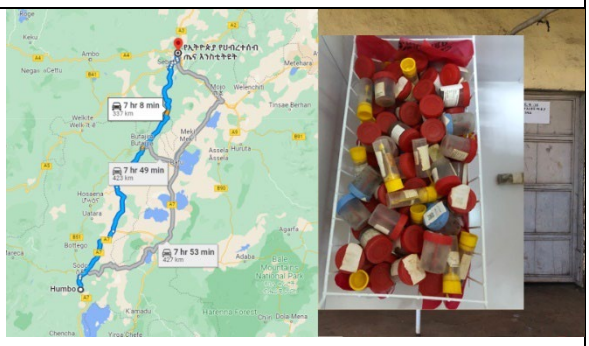
PLOS | NEGLECTED TROPICAL DISEASES

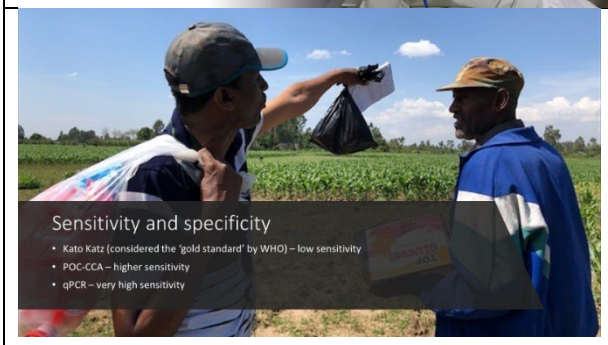
VIEWPOINTS

Is POC-CCA a truly reliable test for schistosomiasis diagnosis in low endemic areas? The trace results controversy

## qPCR

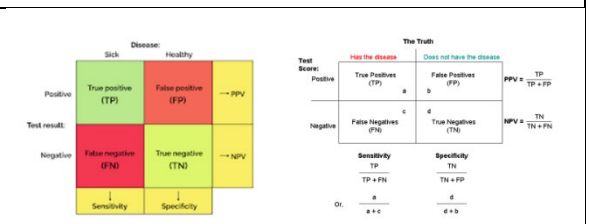
- Nucleic Acid Amplification Test (NAAT): Polymerase Chain Reaction (PCR)
- Qualitative (detected yes/no) or quantitative (Ct values)
- Detects pathogen DNA in stool
- Pros – can potentially detect a single egg, multiplex assays can run multiple targets, potential to quantify infection load
- Cons – eggs encased in hard shell that must be broken open (lysis step), requires expensive equipment, poo is a difficult substance to work with

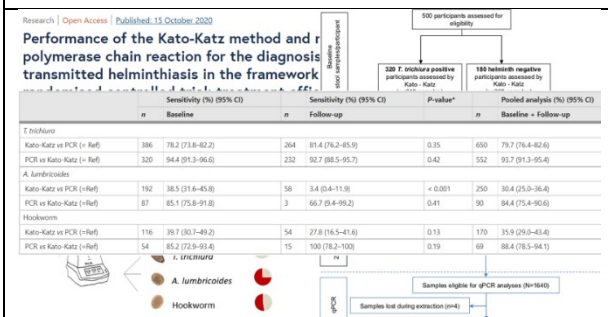



## Sensitivity and specificity

- Kato Katz (considered the 'gold standard' by WHO) – low sensitivity
- POC-CCA – higher sensitivity
- qPCR – very high sensitivity




## Refresher: sensitivity and specificity



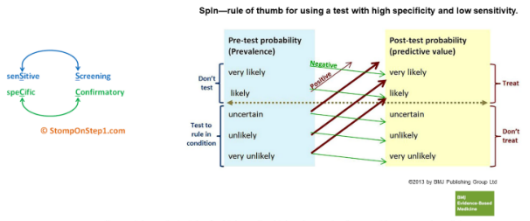
Research | Open Access | Published: 15 October 2020

**Performance of the Kato-Katz method and r polymerase chain reaction for the diagnosis transmitted helminthiasis in the framework**

| | Sensitivity (%) (95% CI) | | Sensitivity (%) (95% CI) | | *P*-value* | | Pooled analysis (%) (95% CI) |
|---|---|---|---|---|---|---|---|
| | *n* | Baseline | *n* | Follow-up | | *n* | Baseline + Follow-up |
| *T. trichiura* | | | | | | | |
| Kato-Katz vs PCR (= Ref) | 386 | 78.2 (73.8–82.2) | 264 | 81.4 (76.2–85.9) | 0.35 | 650 | 79.7 (76.4–82.6) |
| PCR vs Kato-Katz (= Ref) | 320 | 94.4 (91.3–96.6) | 232 | 92.7 (88.5–95.7) | 0.42 | 552 | 93.7 (91.3–95.4) |
| *A. lumbricoides* | | | | | | | |
| Kato-Katz vs PCR (=Ref) | 192 | 38.5 (31.6–45.8) | 58 | 3.4 (0.4–11.9) | < 0.001 | 250 | 30.4 (25.0–36.4) |
| PCR vs Kato-Katz (=Ref) | 87 | 85.1 (75.8–91.8) | 3 | 66.7 (9.4–99.2) | 0.41 | 90 | 84.4 (75.4–90.6) |
| Hookworm | | | | | | | |
| Kato-Katz vs PCR (=Ref) | 116 | 39.7 (30.7–49.2) | 54 | 27.8 (16.5–41.6) | 0.13 | 170 | 35.9 (29.0–43.4) |
| PCR vs Kato-Katz (=Ref) | 54 | 85.2 (72.9–93.4) | 15 | 100 (78.2–100) | 0.19 | 69 | 88.4 (78.5–94.1) |



## How do we apply this when thinking about diagnostics?

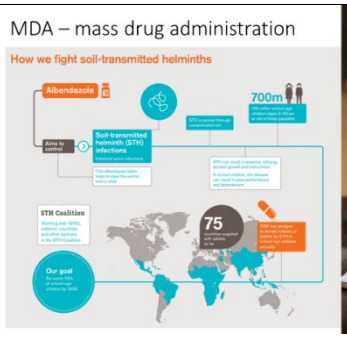


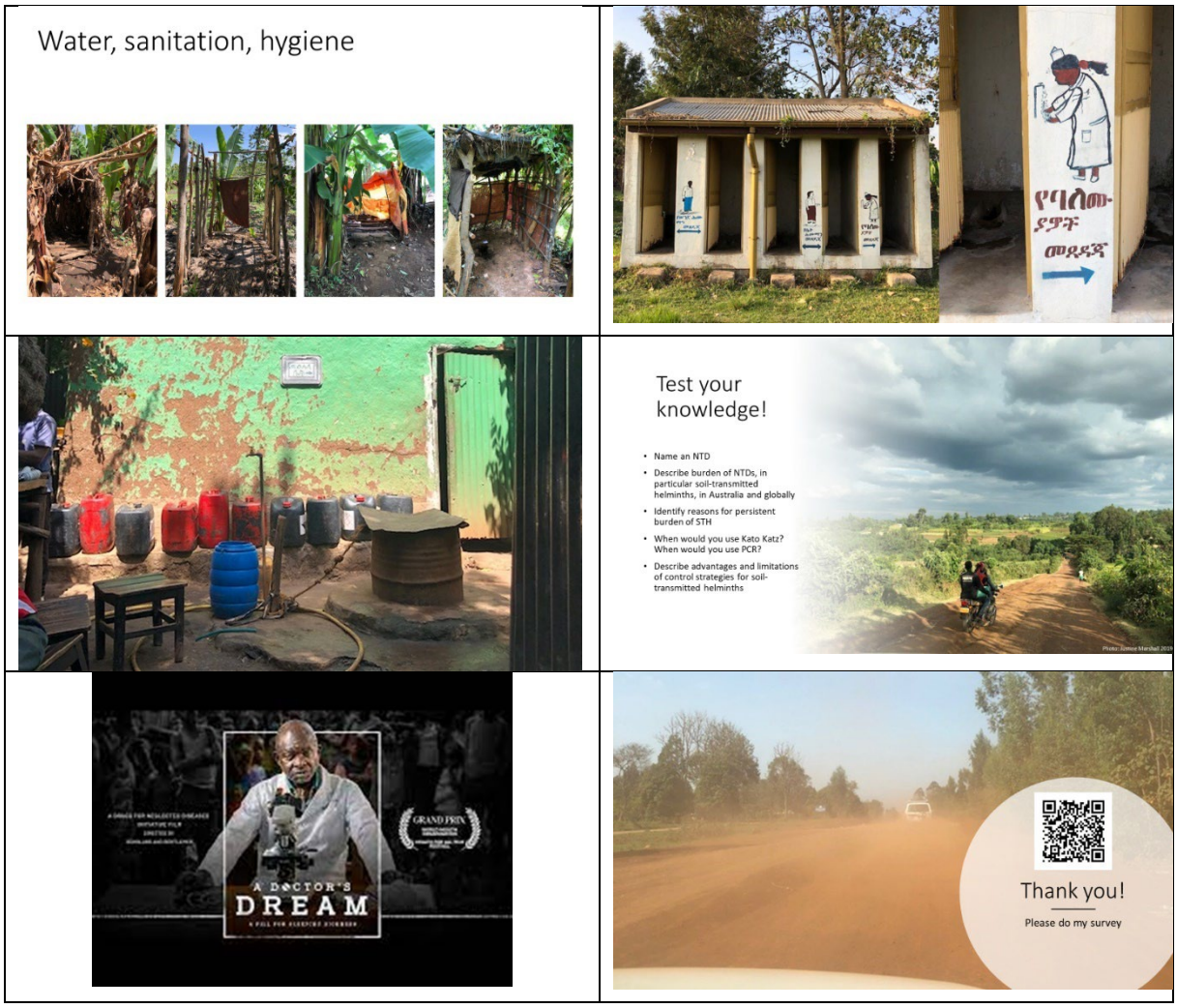

Power M, Fell G, Wright M. "Principles for high-quality, high-value testing." *BMJ Evidence-Based Medicine* 2013;**18**:5-10.

## Strategies for control and elimination

- Mass drug administration – to whom? When?
- WaSH – good intervention for lots of things!
- IEC – information, education and communication
- Test and treat?

## MDA – mass drug administration





Water, sanitation, hygiene
Test your knowledge!
Name an NTD
Describe burden of NTDs, in particular soil-transmitted helminths, in Australia and globally
Identify reasons for persistent burden of STH
When would you use Kato Katz? When would you use PCR?
Describe advantages and limitations of control strategies for soil-transmitted helminths
A DOCTOR'S DREAM
Thank you!
Please do my survey