

Scratching Beneath the Surface: Applied Epidemiology of Vaccine Preventable Diseases in Victoria

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

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DECLARATION OF AUTHORSHIP

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

A handwritten signature in black ink, appearing to read 'M. Marsland', with a stylized, flowing script.

Madeleine Marsland

16 October 2023

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In the words of John Donne, “no man is an island”. I have endeavoured to acknowledge the many superstars involved in each of my projects in relevant chapters. Here, I would like to highlight those who have supported me before, throughout, and likely after my MAE journey.

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ABSTRACT

This thesis describes the projects and experiences I completed to fulfil the requirements of the Australian National University Master of Philosophy in Applied Epidemiology program.

I completed my field placement between February 2022 and December 2023. My placement focussed on vaccine preventable diseases and I was jointly placed in the Communicable Diseases Epidemiology and Surveillance unit and the Immunisation unit at the Victorian Department of Health.

My projects consisted of a descriptive epidemiological analysis of ten years of herpes zoster surveillance data to investigate the impact of the National Shingles Vaccination Program; a serosurvey examining risk factors for Japanese encephalitis virus following an outbreak in an immunologically naïve population; an evaluation of the Australian Rotavirus Surveillance Program in Victoria; the investigation and response to a series of imported measles cases in Victoria following the COVID-19 pandemic; and, the investigation of a vaccine cold chain breach in a Victorian health facility. The findings of these projects supported public health action by informing vaccination policy, improving surveillance systems, and providing a greater understanding of infectious diseases within Victoria.

This thesis also presents additional competencies I completed including literature reviews, conference presentations, peer-reviewed publications and articles submitted to peer-reviewed journals, and my experiences teaching epidemiology. Finally, I describe some of the additional public health activities and experiences I had during my field placement in the program.

ABBREVIATIONS

ABS	Australian Bureau of Statistics
AHPPC	Australian Health Protection Principal Committee
AI	Avian Influenza
AIR	Australian Immunisation Register
ANU	Australian National University
CCB	Cold Chain Breach
CDNA	Communicable Diseases Network Australia
CHO	Chief Health Officer
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DH	Victorian Government Department of Health
DJPR	Victorian Department of Jobs, Precincts and Regions
ED	Emergency Department
ELISA	Enzyme-Linked Immunosorbent Assay
ERP	Expert Review Panel
HR	Hospitalisation Rate
HREC	Human Research Ethics Committee (at ANU unless otherwise specified)
HZ	Herpes Zoster
ICPMR	Institute of Clinical Pathology and Medical Research
ICU	Intensive Care Unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMT	Incident Management Team
IPC	Incoming Passenger Card
IQR	Interquartile Range
IR	Incidence Rate
IRR	Incidence Rate Ratio
JE	Japanese encephalitis
JEV	Japanese encephalitis virus
LFF	Lesson From the Field
LGA	Local Government Area
LPHU	Victorian Local Public Health Unit

MAE	Master of Philosophy in Applied Epidemiology
MMR	Measles, Mumps and Rubella
MVE	Murray Valley Encephalitis
NCIRS	National Centre for Immunisation Research and Surveillance
NIC	National Incident Centre
NIP	National Immunisation Program
NIR	Notification Incidence Rate
NSVP	National Shingles Vaccination Program
PCR	Polymerase Chain Reaction
PHESS	Public Health Event Surveillance System
PHN	Post-Herpetic Neuralgia
PPE	Personal Protective Equipment
RAT	Rapid Antigen Test
SCHN	Sydney Children's Hospital Network
SoNG	Series of National Guidelines
VAED	Victorian Admitted Events Dataset
VDI	Victorian Deaths Index
VEMD	Victorian Emergency Minimum Dataset
VIDRL	Victorian Infectious Diseases Reference Laboratory
VR	Vaccination Rate
VZV	Varicella Zoster Virus

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CHAPTER I

INTRODUCTION

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BACKGROUND

My Master of Philosophy in Applied Epidemiology (MAE) field placement was at the Department of Health, Victoria (DH). DH is the state-wide lead agency for health, and has responsibilities across Health, Ambulance Services, Mental Health and Ageing portfolios. My placement was in the Public Health Division (PHD).

One of the branches within PHD is Health Protection Branch (HPB) and within this sits the Communicable Diseases (CD) section. There are several units within CD:

- Communicable Diseases Epidemiology and Surveillance (CDES)
- Immunisation
- Communicable Disease Prevention and Control (CDPC)
- Victorian Investigation of Complex Sexually Transmitted Infections (VICS)
- Public Health Medicine

My placement focused on Vaccine Preventable Diseases (VPDs) and I primarily worked within CDES (supervised by Janet Strachan), however I also worked across the Immunisation unit (supervised by Rebecca Gang). In addition, I gained broader experience across other communicable disease portfolios. For example, my epidemiological study (chapter 3) focussed on Japanese encephalitis, which sits within the vector-borne diseases portfolio, and I gained experience in a range of infectious disease outbreaks (chapter 7).

In response to the COVID-19 pandemic, the Victorian public health system underwent reform with the establishment of nine new Local Public Health Units (LPHUs). This process commenced prior to my placement and the transition to the new networked public health system continued throughout my placement. This led to changes in some of the day-to-day work of my team during my MAE placement, and also allowed me to work closely with some LPHUs during some of my projects (chapter 3).

MAE COURSE REQUIREMENTS

Projects that I undertook to meet the core and additional competencies required for the MAE are summarised below.

Competency	Chapter				
	2	3	4	5	6
<i>Data analysis</i>	✗				
<i>Epidemiological study</i>		✗			
<i>Evaluate or establish a surveillance system</i>			✗		
<i>Investigate an acute public health problem</i>				✗	
<i>Literature review</i>		✗			
<i>Communication with a lay audience</i>		✗		✗	
<i>Peer-reviewed journal publication</i>	✗	✗		✗	
<i>Conference presentation</i>	✗	✗			
<i>Teaching activities</i>					✗

Core competencies

Analysis of a public health dataset

Chapter 2 details a descriptive epidemiological analysis investigating trends in Herpes Zoster (HZ) between 2012 and 2021 and the impact of the National Shingles Vaccination Program (NSVP) in Victoria.

In 2016, Australia implemented the NSVP, recommending adults aged ≥ 60 years receive HZ vaccination, and providing funded HZ vaccination to adults aged 70 – 79 years under the National Immunisation Program (NIP). I conducted epidemiological analyses of HZ case notifications, emergency department presentations, hospitalisations, deaths and vaccinations over ten years (2012 – 2021). These analyses included approximately five years of data prior to and following the implementation of the NSVP, for adults aged ≥ 60 years in Victoria. The findings suggested the NSVP has influenced the epidemiology of HZ for adults eligible for funded HZ vaccination (70 – 79 years), however there has been less of an impact on other age groups recommended to be vaccinated but not eligible for funded vaccination (60 – 69 years and 80+ years). This is likely due to low vaccination rates across all age groups, but particularly in ages that are not eligible for funded vaccination. The results were presented at conferences and published in [Communicable Diseases Intelligence](#).

Design and conduct an epidemiological study

Chapter 3 details my epidemiological study, a serosurvey of Japanese encephalitis virus (JEV) conducted in an immunologically naïve population.

In early 2022, the first outbreak of Japanese encephalitis (JE) was reported in south-eastern Australia. As most JEV infections are asymptomatic, it was thought that thousands of people may have been infected during the outbreak. I co-lead a serosurvey in northern Victoria to investigate the extent of infection and risk factors for infection in an immunologically naïve population. The results showed that many people in northern Victoria may have been infected with JEV during the outbreak and there remains widespread population vulnerability to infection with JEV. Older age and exposure to feral pigs were the only investigated factors significantly associated with infection. The results suggested that a widespread vaccination program may be required in the future to prevent further infections. This serosurvey supported a national body of JEV serosurveillance work and the results informed the progressive expansion of vaccine eligibility in south-eastern Australia. The results of the study have been accepted for publication in the Medical Journal of Australia. The findings were also presented at conferences.

Evaluation or establishment of a surveillance system

Chapter 4 outlines my evaluation of the Victorian component of the Australian Rotavirus Surveillance Program (ARSP).

In late 2022, DH commenced discussions with the Murdoch Children's Research Institute (MCRI), who operate the ARSP, to consider opportunities to support and enhance the ARSP in Victoria. Using the Centers for Disease Control and Prevention (CDC) Guidelines for Evaluating Public Health Surveillance Systems, I conducted an evaluation of the ARSP for Victoria to understand the strengths and weaknesses of the program and opportunities for enhancement. The evaluation found that the ARSP is a simple, acceptable and flexible surveillance system, but that there are opportunities to improve its stability and the representativeness of Victorian samples, and to better integrate the ARSP into DH systems. The report and recommendations were provided to the ARSP and DH. As at the time of submission, DH is actively considering next steps to enhance rotavirus surveillance in Victoria.

Investigation of an acute public health problem or threat

Chapter 5 outlines two investigations I was involved in during the MAE program.

In Part A, I present a case series of several imported measles cases that occurred in Victoria, after the international border was reopened following the COVID-19 pandemic. I was involved in the investigations of six imported measles cases, three of which were single cases and three of which were a household cluster. I developed a case series of lessons learned from these investigations, to support future responses locally in Victoria and across Australia. The findings were published in [Communicable Diseases Intelligence](#).

In Part B, I describe an investigation of a vaccine cold chain breach (CCB) that occurred in a Victorian health facility in 2023. A self-audit was conducted to identify the cause of the CCB and other opportunities to improve vaccine storage at the health service. A total of 64 impacted patients were identified and offered re-vaccination as part of the investigation and response to this acute public health event. The results were provided to the Immunisation unit to support continuous improvement of the management of future CCBs.

In addition to these investigations, I was able to gain experience responding to a wide range of notifiable diseases in Victoria, and a high-level summary of these experiences is provided at Chapter 7. Furthermore, the JEV serosurvey, discussed at Chapter 3, also directly contributed to investigating an acute public health problem and informing control measures, further demonstrating this skillset.

Additional competencies

Literature review

I co-lead a literature review on JE in immunologically naïve populations, which informed my epidemiological study and was published in the [Australian New Zealand Journal of Public Health](#), and is reproduced in full at Chapter 3. Unstructured literature reviews were conducted for all other MAE projects included in this thesis.

Lay summary

I developed several lay summaries in relation to the JEV serosurvey (Chapter 3):

- Information sheets for participants explaining their individual results; and
- A lay summary of provisional results from the JEV serosurvey that was published on the DH website and in a media release.

I also developed a lay summary to support the vaccine CCB investigation (Chapter 5) providing information for Frequently Asked Questions for impacted patients.

Peer-reviewed publications

I published the following peer-reviewed publications during the MAE:

- Marsland MJ, Glynn-Robinson A, Gang R, Strachan J. The impact of the National Shingles Vaccination Program on the epidemiology of Herpes Zoster among adults ≥ 60 years in Victoria, Australia. *Communicable Diseases Intelligence*. 2023 Sep;47. Doi: 10.33321/cdi.2023.47.56 (Chapter 2)
- Thomson TN, Marsland MJ, Minko C, Snow KJ, Friedman ND. Japanese encephalitis: a rapid review of reported prevalence of infection, clinical disease and sequelae in immunologically naïve populations to inform Australia's response. *Aust N Z J Public Health*. 2023 Apr;47(2):100041. Doi: 10.1016/j.anzjph.2023.100041 (Chapter 3)
- Marsland MJ, Thomson TN, O'Brien H, Peach E, Bellette J, Humphreys N, McKeon C-A, Cross W, Moso MA, Batty M, Nicholson S, Karapanagiotidis T, Lim CK, Williamson D, Winkler N, Koirala A, Macartney K, Glynn-Robinson A, Stewart T, Minko C, Snow K, Black J, Friedman ND. Serosurvey for Japanese encephalitis virus and related flaviviruses following an outbreak in an immunologically naïve population, Victoria, Australia (accepted for publication in the *Medical Journal of Australia*) (Chapter 3)
- Marsland MJ, Strachan J, Gang R, O'Hara M, Hughes N, Glynn-Robinson A. Lessons from the re-emergence of imported measles cases following the COVID-19 pandemic in Victoria, Australia. *Communicable Diseases Intelligence*. 2023 Sep;47. Doi: 10.33321/cdi.2023.47.54 (Chapter 5)

In addition, I was listed as a co-author on the following peer-reviewed publication:

- Kinsella P, Moso M, Martin G, Karapanagiotidis T, Karamalakis D, Nicholson S, Batty M, Jackson K, Marsland MJ, Thomson TN, Manoharan L, O'Brien H, Friedman ND, Bond K, Williamson DA, Lim CK. Laboratory Evaluation of ELISA and Indirect Immunofluorescence Assay in Response to Emergence of Japanese Encephalitis Virus Genotype IV in Australia. *Journal of Clinical Virology*. 2023;168:105580. Doi: 10.1016/j.jcv.2023.105580

Conference presentations

I delivered the following oral presentations at the Communicable Diseases & Immunisation Conference, Perth, Australia, 19 to 21 June 2023 and at the South Asia Field Epidemiology and Technology Network (SAFETYNET) Conference, Canberra, Australia, 12 to 15 September 2023:

- Marsland MJ, Glynn-Robinson A, Gang R, Strachan J. Impact of the National Shingles Vaccination Program on Zoster epidemiology in Victoria. (Chapter 2)
- Marsland MJ, Thomson T, O'Brien H, Lim CK, Gang R, Strachan J, Glynn-Robinson A, Friedman ND. Demographic and behavioural risk factors for Japanese encephalitis virus infection in Victoria. (Chapter 3)

In addition, I was listed as a co-author and helped develop the following conference presentations:

- Winkler NE, Koirala A, Hirani R, Hueston L, Baker J, O'Sullivan M, Kaur G, Prasad S, Dwyer DE, Hoad V, Gosbell IB, Irving DO, Lambert S, Baldwin Z, Glasgow K, Thomson T, Marsland M, Friedman ND, Smoll N, Khandaker G, Kitchener S, Chor J, Hayward C, Beazley R, Flood L, Hinchcliff A, Nelson J, Currie BJ, and Macartney K on behalf of the Australian Japanese encephalitis virus serosurvey group. Serosurveillance to assess Japanese encephalitis virus infection following its emergence in Australia.
 - Australasian Society for Infectious Diseases Annual Scientific Meeting, 2023.
 - Communicable Diseases & Immunisation Conference, 2023.
- Thomson T, Marsland M, O'Brien H, Lim CK, Easton M, Stewart T, Friedman ND. Serological evidence of Japanese encephalitis virus infection across northern Victoria, 2022.
 - Communicable Diseases & Immunisation Conference, 2023.
 - South Asia Field Epidemiology and Technology Network (SAFETYNET) Conference, 2023.
- O'Hara M, Strachan J, Hughes N, Marsland M, Friedman D. Measles in 2023: how does investigation and response differ from pre-pandemic times?
 - Communicable Diseases & Immunisation Conference, 2023.

Teaching activities

Chapter 6 details teaching exercises I developed and delivered during the MAE program:

- Lesson from the field: Responding to an outbreak of a new or emerging threat (Chapter 6)
- First year teaching session: Age standardisation (Chapter 6)

I also supported delivering an 'epidemiology refresher' to final year Public Health Physician registrars in Victoria in preparation for their examinations.

CHAPTER II

ANALYSIS OF A PUBLIC HEALTH DATASET

The impact of the National Shingles Vaccination Program on
the epidemiology of Herpes Zoster among adults ≥ 60 years in
Victoria, Australia

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PROLOGUE

Study rationale

The National Shingles Vaccination Program (NSVP) has been operating in Australia since November 2016, however few studies have investigated its impact on the epidemiology of herpes zoster (HZ) in Australia. This study aimed to better understand the impact the NSVP had on the epidemiology of HZ in Victoria and identify potential opportunities for improvement to support Victoria's immunisation policy and planning.

My role

In collaboration with my supervisors, I developed the study protocol and data analysis plan for this project. My supervisors extracted and de-identified data for me to analyse. I completed the data analysis using Stata v16 and Microsoft Excel (2022), and wrote the project up for publication.

Lessons learned

This was the first project I completed as part of the MAE program. Having limited prior experience analysing quantitative data, this was an opportunity to develop these skills and gain confidence in using a statistical software package such as Stata.

I learned about different statistical methods and the importance of choosing valid methods, such as not comparing data collected across different datasets. This project taught me about the limitations of routinely collected surveillance data and the importance of understanding data quality when reporting outcomes. I had to redo parts of my analysis after data fixes occurred, changing the extracted data. I also learned how underreporting and changes in testing practices can impact surveillance data. This demonstrated the value of having good quality data for program evaluation and considering the many possibilities of why data was changing over time, which may not have been associated with the intervention under investigation, and the role of artefact.

This project taught me the importance of being flexible during the MAE program. I initially aimed to compare the epidemiology between vaccinated and unvaccinated HZ cases by linking notification, hospitalisation and death data to vaccination status using the Australian Immunisation Register (AIR). However, there were internal legal concerns about using linked data in research which meant that this was not feasible.

Finally, through this project I learned about different ways of presenting data to different audiences, as I presented this project at conferences, to internal decision-makers, and prepared a peer reviewed publication. The publication was particularly challenging as I needed to select an appropriate journal and develop clear and concise outcomes relevant to a broad audience. This showed me the difficulties faced when undertaking a project for both research and policy purposes.

Public health implications

This study supports a greater understanding of trends in HZ epidemiology in Victoria and the impact of the NSVP. The findings may be of use at a national level to inform policy, vaccination strategies, and other interventions for HZ. Findings were shared with the Victorian Department of Health Immunisation and Communicable Diseases Epidemiology Surveillance units, and with relevant teams at the Australian Government Department of Health and Aged Care, through sharing of the publication and presenting at relevant unit meetings. Results were presented at the Communicable Diseases & Immunisation Conference in Perth 2023 and at the South Asia Field Epidemiology and Technology Network (SAFETYNET) Conference in Canberra 2023 (Appendix A). This included discussing outcomes with interstate and international policy makers to support their vaccination policy decision making. Results were published in [Communicable Diseases Intelligence](#), and are reproduced in full in this chapter.

Acknowledgements

I would like to thank my field supervisors Janet Strachan and Rebecca Gang for identifying this project, providing extensive feedback and technical support, and supporting further investigations based on the initial findings. I would like to thank my academic supervisor Anna Glynn-Robinson for her guidance as I completed my first MAE competency, and for supporting my understanding of some of the statistical elements of this project that were new to me. I would like to thank the laboratory liaison staff in CDES for investigating changes in HZ testing over time and all of the laboratories who contributed to this work.

PEER REVIEWED PUBLICATION:
THE IMPACT OF THE NATIONAL SHINGLES VACCINATION
PROGRAM ON THE EPIDEMIOLOGY OF HERPES ZOSTER
AMONG ADULTS ≥ 60 YEARS IN VICTORIA, AUSTRALIA



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The impact of the National Shingles Vaccination Program on the epidemiology of herpes zoster among adults ≥ 60 years in Victoria, Australia

Madeleine J Marsland, Anna Glynn-Robinson, Rebecca F Gang, Janet Strachan

Abstract

Introduction

In November 2016, Australia recommended herpes zoster (HZ) vaccination for adults aged ≥ 60 years and implemented a National Shingles Vaccination Program (NSVP) offering free HZ vaccination to adults aged 70–79 years. This study investigated trends in HZ epidemiology among Victorian adults aged ≥ 60 years and the impact of the NSVP in this population.

Methods

We conducted epidemiological analyses of routinely collected HZ surveillance data for Victorian adults aged ≥ 60 years who were notified as having a HZ illness or vaccination between 2012 and 2021. Annual incidence rates are presented for vaccinations, case notifications, emergency department presentations, hospitalisations and deaths by five-year age groups. Age-specific incidence rate ratios are calculated comparing the period prior to (1 January 2012 to 31 October 2016) and following (1 November 2016 to 31 December 2021) NSVP implementation.

Results

HZ vaccination rates were highest among those eligible to receive free vaccination (70–79 years), but appear to have plateaued across all age groups and remained below full coverage. Incidence rate ratios showed a statistically significant increase ($p < 0.01$) in HZ notifications across all age-groups. Emergency presentations and hospitalisations showed a statistically significant decline ($p < 0.05$) among the 70–79 year old age groups; however, these rates remained consistent or increased among other age groups for whom vaccination is recommended. Mortality rates declined, particularly among those aged 85+ years.

Discussion

HZ continues to cause significant disease among the older adult population in Victoria. The findings of this study suggest the NSVP has led to some changes in the epidemiology of HZ among the 70–79 years old age group in Victoria; however, there is less evidence that it has influenced other age groups for whom vaccination is recommended. An evaluation of the NSVP and epidemiology of HZ at a national level is required to identify strategies to improve vaccination coverage among the target populations.

Keywords: Herpes zoster; herpes zoster vaccine; vaccine-preventable diseases; epidemiology

Introduction

Herpes zoster (HZ), commonly known as shingles, is a reactivation of varicella zoster virus (VZV) infection. The incidence of HZ is increasing globally among unvaccinated populations.¹ The lifetime risk of HZ is approximately one in three,^{2,3} with incidence and complication rates highest amongst older adults.^{1,2}

There are two HZ vaccines approved for use within Australia: Zostavax, a live-attenuated single-dose HZ vaccine, and Shingrix, a recombinant vaccine containing VZV glycoprotein E antigen given as a two-dose schedule two to six months apart.^{2,4} Zostavax has been available in Australia since 2006, whilst Shingrix was registered for use in the private market in 2021.^{2,4} Shingrix has greater effectiveness across all age groups, particularly among older adults aged ≥ 80 years, for whom Zostavax has very poor effectiveness.^{3–5} Shingrix is also considered a safer vaccine and is recommended for immunocompromised individuals.³ Protection from Shingrix is thought to last for at least 10 years, whereas Zostavax effectiveness wanes within 5–10 years.³

In November 2016, Australia implemented a National Shingles Vaccination Program (NSVP). The Australian Technical Advisory Group on Immunisation recommended HZ vaccination for all adults aged ≥ 60 years, with Zostavax to be provided free-of-charge under the National Immunisation Program (NIP) to adults aged 70 years, and a time-limited catch-up program implemented for adults aged 71–79 years (until October 2023).^{3,6,7} In 2022, HZ vaccine recommendations were expanded to include immunocompetent adults aged ≥ 50 years and severely immunocompromised individuals aged ≥ 18 years.³ In 2023, the Australian Government announced that Shingrix would replace Zostavax on the NIP, with funded vaccination for all adults aged 70 years, for Aboriginal and Torres Strait Islanders aged 50 years and over, and for severely immunocompromised adults aged ≥ 18 years meeting specified criteria.⁸

To date, few studies have examined the impact of the NSVP in Australia.^{9–16} Early studies found a significant decline in the incidence of HZ in the first two to three years following implementation.^{10,12,13} However, these studies also suggested waning immunity may impact vaccine effectiveness and noted the need for further evaluations.^{10,12,13} There remains limited evidence regarding the long term impact of the NSVP.⁴

We investigated trends in HZ epidemiology among Victorian adults aged ≥ 60 years before and after implementation of the NSVP.

Methods

Data from 2012–2021 were extracted for persons aged ≥ 60 years, with those aged 70–79 years considered ‘NIP-eligible’. This included 58 months of data prior to implementation of the NSVP (1 January 2012 to 31 October 2016: ‘pre-NSVP’) and 62 months of data following implementation (1 November 2016 to 31 December 2021: ‘post-NSVP’).

De-identified individual vaccination data were sourced from the Australian Immunisation Register (AIR) for both Zostavax and Shingrix vaccinations. Data on vaccines distributed under the NIP were sourced from internal Victorian Department of Health data. Analysis of vaccination data is focussed on the post-NSVP period, as there was low vaccine uptake and poor data quality during the pre-NSVP period.

De-identified HZ case notifications were sourced from the Victorian Public Health Event Surveillance System (PHESS) and included ‘probable’ (clinical evidence only) and ‘confirmed’ (clinical and laboratory evidence) varicella zoster (shingles) notifications,¹⁷ and varicella (unspecified) notifications.¹⁸ Zoster is a routine notifiable condition in Victoria, with notification required by medical practitioners and pathology services within five days of diagnosis.¹⁹ By including varicella unspecified cases (i.e. notifications based on laboratory evidence without clinical notification), there is a risk

of including chickenpox cases in the analysis. However, as few people in the age groups investigated would have been experiencing their primary varicella infection, excluding this varicella classification would have led to an undercount of case notifications. HZ testing data were sourced from internal Victorian Department of Health data by surveying Victorian public and private laboratories.

De-identified data on emergency department (ED) presentations and hospitalisations were sourced from the Victorian Emergency Minimum Dataset (VEMD) and the Victorian Admitted Episodes Database (VAED) using the *International Statistical Classification of Diseases and Related Health Problems, tenth revision, Australian Modification* (ICD-10-AM) code B02 (Zoster). Mortality data were sourced from the Registry of Births, Deaths and Marriages Victoria – Victorian Deaths Index (VDI) using the search terms ‘varicella OR shingles OR zoster OR herpes OR herpetic OR VZV (excluding records with simplex)’ as cause of death. Individuals were considered to have presented or died ‘due to’ HZ if their coded primary diagnosis or direct cause of death was HZ-related, and ‘with’ HZ if the ‘other’ or ‘antecedent’ listed condition or cause of death was HZ-related.

Age, sex and locality (Local Government Area or postcode) were extracted from all datasets, except vaccine distributions and laboratory testing survey data. Where age or confirmation of Victorian residence (locality) was not available, data were excluded. Data analyses were undertaken using Stata v.16²⁰ and Microsoft Excel (2022). All datasets were descriptively analysed to identify changes over time and to produce summary statistics, including medians and interquartile ranges (IQRs).

Age-specific rates were calculated for each year (2012–2021) using mid-year Estimated Resident Populations (ERPs) from the Australian Bureau of Statistics (ABS)²¹ and expressed as rates per 100,000 population per year. Rates and incidence rate ratios (IRRs) with 95% confidence intervals (CI) were calculated using Poisson

regression to compare the pre-NSVP period to the post-NSVP period and expressed as rates per 100,000 person-years by age group. *P* values were derived using the chi-square test. Crude test positivity rates were calculated by dividing the number of case notifications (PHESS) by the total HZ tests per year. Direct age standardisation was used to compare rates by sex using the Australian standard population 2001.²¹

Ethics approval was granted by the Australian National University Human Research Ethics Committee (protocol 2022/266).

Results

Vaccinations

There were 302,667 individuals with HZ vaccinations recorded in the AIR, most (99.2%) of which occurred post-NSVP (Table 1). Vaccination rates (VRs) pre-NSVP were negligible (Table 2).

Following the NSVP implementation, VRs increased across all age groups. However, VRs were consistently substantially higher in the NIP-eligible population (Figure 1A) than in the NIP-ineligible population (Figure 1B). Overall, females had a slightly higher age-standardised VR than did males, with VRs of, respectively, 2,529 and 2,325 per 100,000 population over the study period.

In 2016, VRs were highest in the 75–79 years age group, particularly those aged 78 and 79 years (Figure 1A; Table 3). From 2017, VRs were highest in the 70–74 years age group, with the highest VR in those aged 70 years (Table 3). VRs declined across all age groups from 2017 to 2020 before slightly increasing in 2021 (Figure 1A; Table 3; Figure 1B). VRs appear to have plateaued and remain low across all age groups, and are consistently lower among the age groups recommended to be vaccinated but not NIP-eligible (Figure 1B).

Table 1: Counts and characteristics of herpes zoster related cases, emergency department presentations, hospitalisations, deaths and vaccinations, prior to and following implementation of the National Shingles Vaccination Program (NSVP)

Category	Value	Notified cases ^a		ED presentations ^{a,b}		Hospitalisations ^{a,b,c}		Deaths ^{a,d,e}		Persons vaccinated ^{a,f}	
		Pre-NSVP	Post-NSVP	Pre-NSVP	Post-NSVP	Pre-NSVP	Post-NSVP	Pre-NSVP	Post-NSVP	Pre-NSVP	Post-NSVP
Age group (years)	60–64	2,335	4,598	923	1,330	248	351	≤5	≤5	370	7,486
	65–69	2,288	2,702	931	1,394	335	444	≤5	≤5	621	11,744
	70–74	1,732	3,112	851	1,029	348	394	≤5	7	549	187,614
	75–79	1,474	2,099	784	774	411	435	14	6	692	82,160
	80–84	1,089	1,825	645	743	513	512	12	13	158	6,845
	85+	1,283	2,572	710	896	759	1,122	69	57	129	4,299
Sex	Male	4,366	7,896	2,219	2,755	1,079	1,249	37	36	982	137,196
	Female	5,814	10,961	2,625	3,411	1,535	2,009	64	52	1,537	162,941
	Not specified	21	51	0	0	0	0	0	0	0	11
Total		10,201	18,908	4,844	6,166	2,614	3,258	101	88	2,519	300,148

a Pre-NSVP: pre-implementation of the National Shingles Vaccination Program (NSVP), 1 January 2012 to 31 October 2016; Post-NSVP: post-implementation of the NSVP, 1 November 2016 to 31 December 2021.

b Notification where HZ listed as a primary reason for presentation.

c Mandatory reporting for public and private hospitals came into effect in September 2013.

d Counts of ≤ 5 were withheld to protect individual privacy.

e Notification where HZ listed as a primary cause of death.

f Based on first dose of HZ vaccine given.

Table 2: Crude notification incidence rates, emergency department presentation rates, hospitalisation rates, mortality rates and vaccination rates per 100,000 population per year for adults aged ≥ 60 years in Victoria, 2012 to 2021

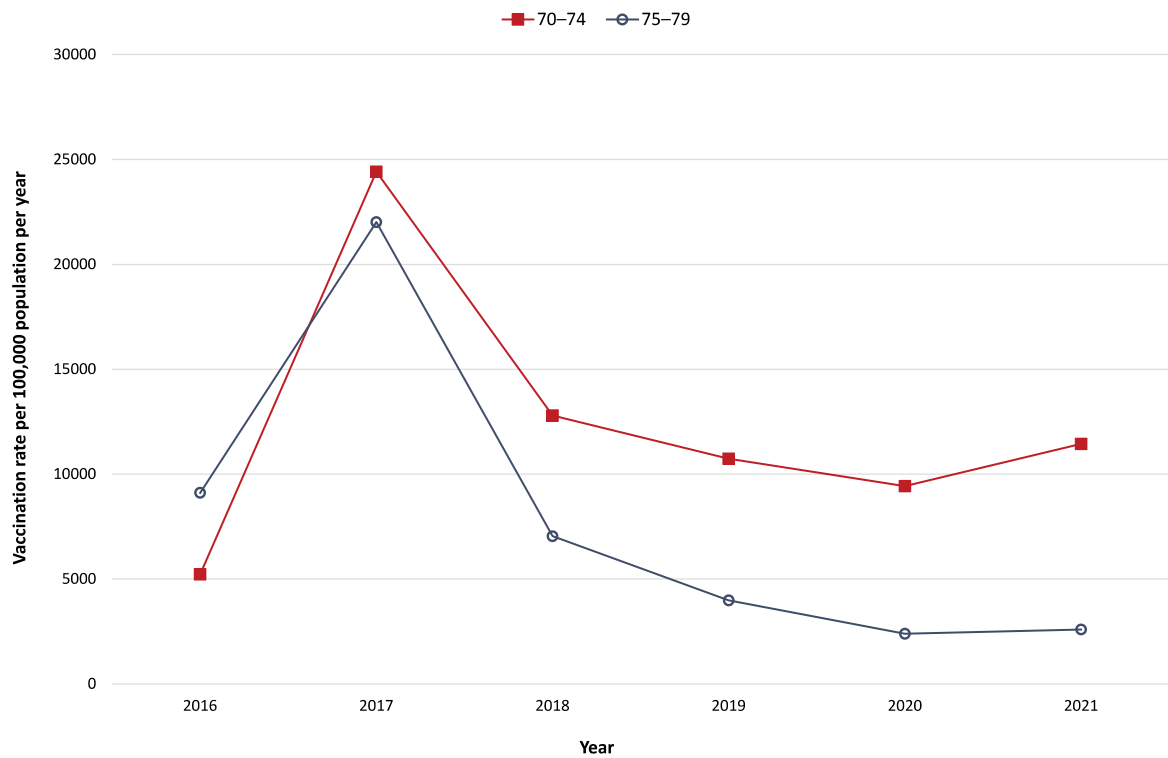
Year	Crude rate per 100,000 population per year for adults ≥ 60 years				
	Notification incidence rate	Emergency department presentation rate	Hospitalisation rate	Mortality rate	Vaccination rate
2012	139.4	91.7	52.2	1.7	2.0
2013	159.2	84.5	42.8	2.4	5.2
2014	177.8	81.9	44.3	2.0	26.0
2015	189.7	86.2	45.2	1.2	47.5
2016	233.6	84.1	45.6	1.8	2,270.5
2017	244.7	79.9	47.3	1.8	8,120.0
2018	261.9	85.6	51.3	1.3	3,879.8
2019	270.5	88.2	47.5	0.8	2,927.2
2020	270.1	85.8	44.2	1.1	2,384.8
2021	293.4	94.7	41.0	1.2	2,976.1

Table 3: Age specific vaccination rates per 100,000 population per year for 70–79 year-olds (NIP- eligible population) in Victoria, 2016 to 2021

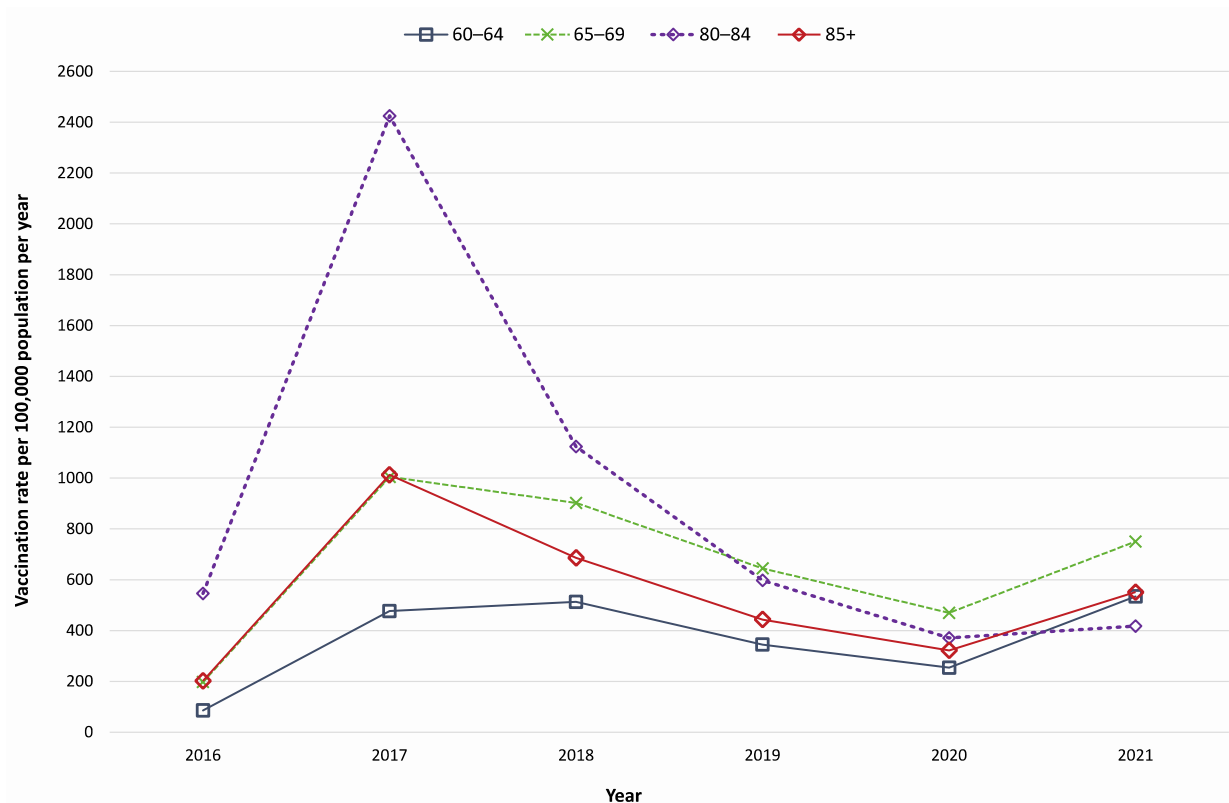
Age (years)	Vaccination rate per 100,000 population per year					
	2016	2017	2018	2019	2020	2021
70	4,713	31,119	28,485	28,852	26,549	28,759
71	4,954	22,247	10,004	8,976	8,251	12,107
72	5,191	22,212	7,882	5,205	4,809	7,127
73	5,676	22,101	7,487	4,314	3,334	4,726
74	5,780	22,272	6,983	4,227	2,550	3,277
75	6,383	22,850	7,744	4,795	2,779	3,032
76	6,804	22,314	6,721	4,025	2,480	2,668
77	7,764	21,566	6,674	3,430	2,210	2,333
78	10,157	22,020	6,807	3,416	2,075	2,328
79	15,654	21,068	7,198	4,091	2,304	2,484

Figure 1: Age-specific rates of HZ vaccinations aged 60 years and over by 5-year age groups, Victoria, Australia 2016–2021

A: NIP-eligible age groups, ages 70–79 years



B: NIP-ineligible age groups, ages 60–69 and 80+ years



Across July–December 2021, the count of individuals vaccinated with Shingrix gradually increased. Zostavax predominated, particularly among those aged 70–74 (96.9% Zostavax, 3.1% Shingrix) and 75–79 years (93.8% Zostavax, 6.2% Shingrix). There was higher uptake of Shingrix among other age groups, particularly among those aged 60–64 years (50.2% Zostavax, 49.8% Shingrix) and 65–69 years (58.2% Zostavax, 41.8% Shingrix).

AIR data indicated most persons only received one HZ vaccine dose ($n = 296,174$), with 294,027 receiving a single Zostavax, and 2,147 receiving a single Shingrix. Of those who received multiple HZ vaccine doses ($n = 6,493$), the most common combination was two doses of Zostavax ($n = 5,545$), with other combinations far less frequent: two doses of Shingrix ($n = 566$), Zostavax followed by Shingrix ($n = 258$), Zostavax followed by two doses of Shingrix ($n = 59$), and three doses of Zostavax ($n = 54$). Other dose combinations, while reported, accounted for less than 0.2% of recipients (11/6,493). Of the 3,041 who received Shingrix, 1,595 were eligible to receive a second dose during the study period (first dose received more than two months before study conclusion), and 627 (39.3%) were fully vaccinated. The recommended time interval between Shingrix doses is two to six months. The median time interval between doses was 70 days (IQR: 63–84 days).

Internal vaccine distribution data, for vaccines intended for use by the NIP-eligible population, were compared with AIR vaccination data. Across 2016 and 2017, approximately double the number of herpes zoster doses recorded in AIR ($n = 276,159$) were distributed across Victoria ($n = 525,035$). However, the discrepancies between these two datasets have narrowed in subsequent years (2018 to 2021).

Case notifications

There were 29,109 cases notified over the period (Table 1): 27.4% (7,985/29,109) were ‘varicella herpes zoster’ and 72.6% (21,124/29,109) were ‘varicella unspecified’. Age-standardised rates

showed females had a slightly higher average notification incidence rate (NIR) than males, 239.0 compared with 202.7 per 100,000 population over the study period.

Annual crude NIRs increased between 2012 and 2021 from 139.4 to 293.4 per 100,000 per year (Table 2). Age-specific NIRs steadily increased among most age groups under investigation and were highest amongst adults aged 85+ years (Figure 2). However, NIRs for the 70–74 and 75–79 years age groups both declined between 2016 and 2018, from 242.2 to 205.9 per 100,000 population per year and from 237.2 to 198.8 per 100,000 population per year respectively, and remained below 2016 levels before rising and peaking in 2021 (Figure 2). When comparing NIRs between the pre-NSVP and post-NSVP periods, there was a statistically significant increase in zoster notifications post-NSVP in all age groups ($p < 0.001$) (Table 4).

The total number of HZ tests performed in Victoria rose between 2012 and 2021, with a peak in testing occurring in 2019 (Figure 3). The crude test positivity also rose during this period.

Emergency department presentations

There were 11,825 HZ-related ED presentations recorded, of which 11,010 (93.1%) were coded as presenting due to HZ (primary illness) (Table 1). Age-standardised rates comparing sex were similar for females and males, respectively at 84.7 and 87.3 per 100,000 population over the study period.

Crude ED rates remained consistent over the study period (Table 2), with age-specific ED rates declining among the 70–74, 75–79 and 80–84 years age groups but increasing among the 60–64 and 65–69 years age groups (Figure 4). Incidence rate ratios comparing the pre-NSVP to the post-NSVP period showed statistically significant decreases for the 70–74 and 75–79 years age groups, and statistically significant increases for the 60–64 and 65–69 years age groups (Table 4).

Figure 2: Age-specific rates of HZ notified cases aged 60 years and over by 5-year age groups, Victoria, Australia 2012–2021

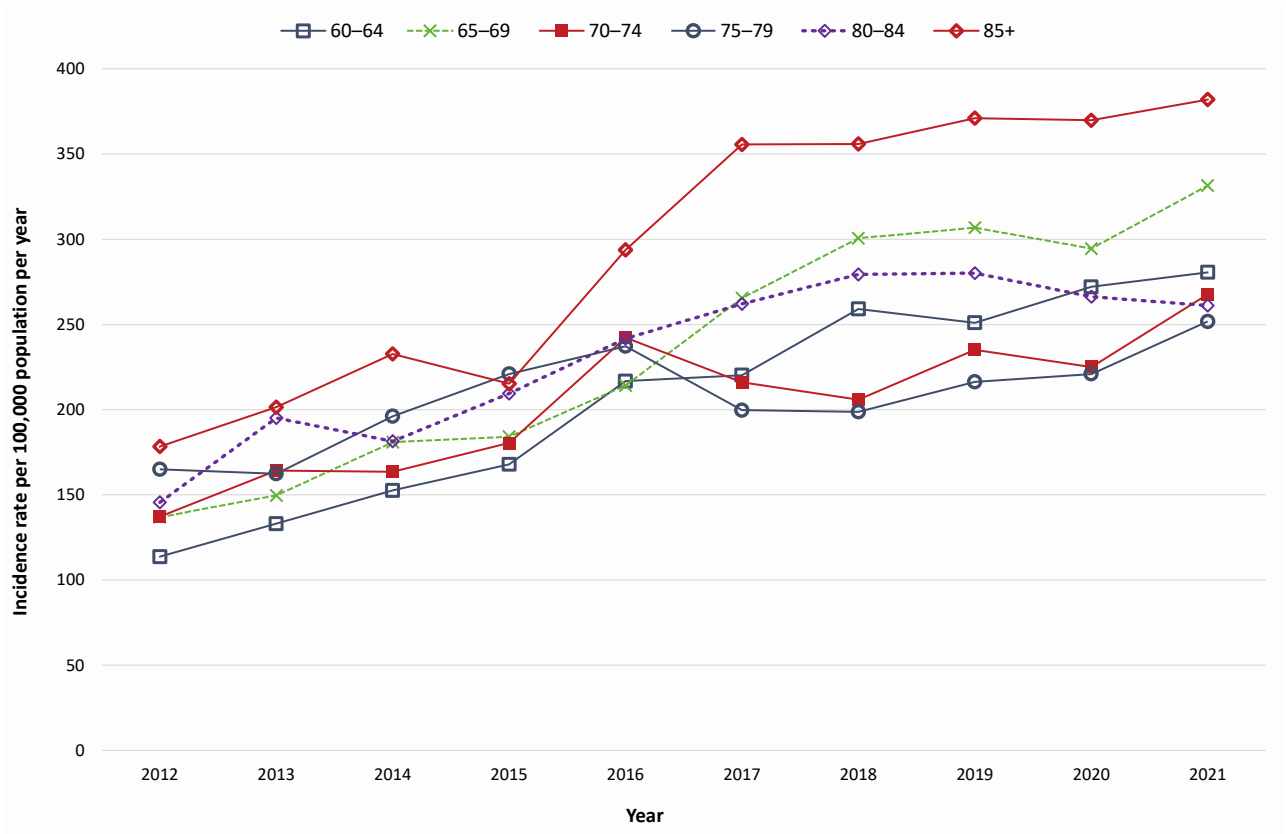


Figure 3: HZ tests conducted by Victorian laboratories and crude test positivity rate, 2012 to 2021

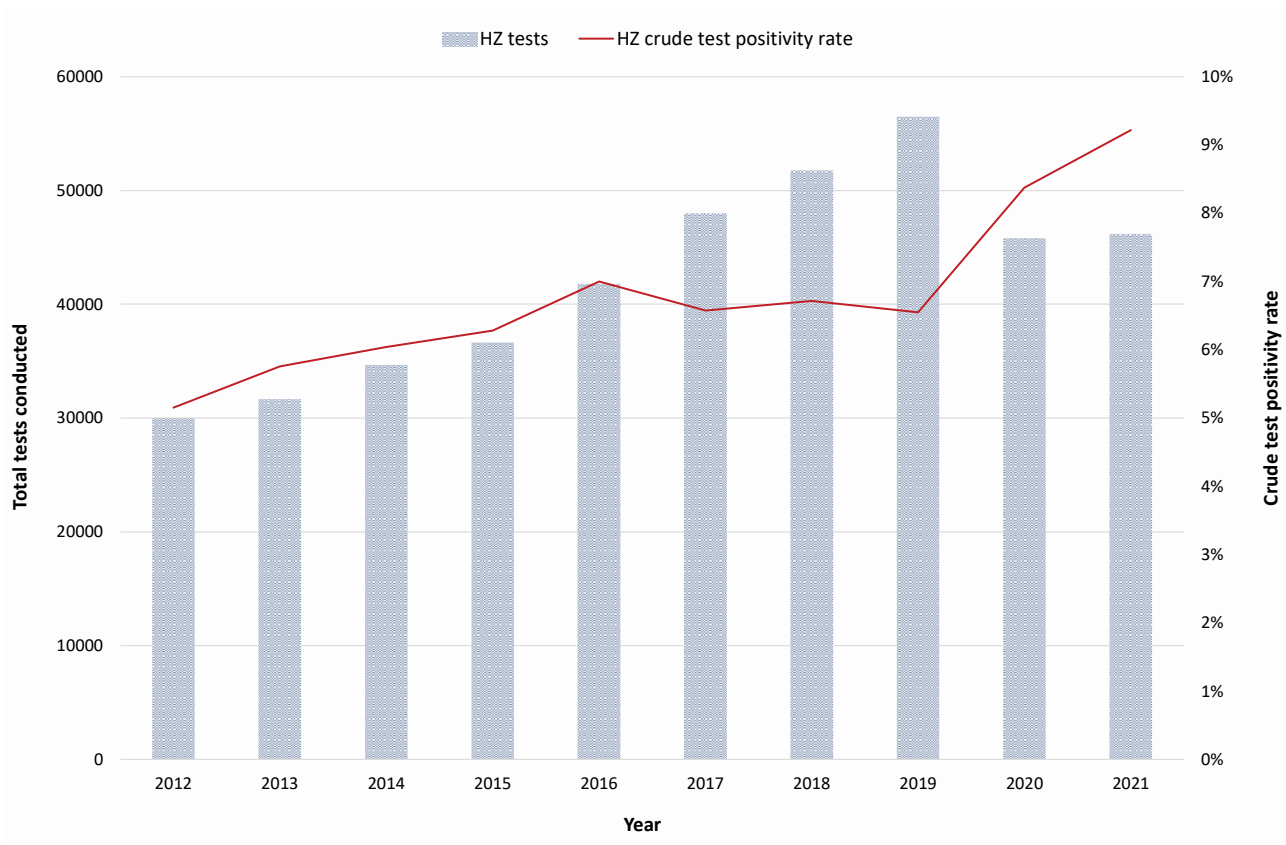


Table 4: Rates and incidence rate ratios comparing prior to and following implementation of the National Shingles Vaccination Program (NSVP) for cases, emergency department presentations and hospitalisations by five-year age groups

Category	Age group (years)	Pre-NSVP incidence rate ^{a,b}	Post-NSVP incidence rate ^{a,b}	Comparison		
				IRR ^c	95% CI ^d	p value
Case notifications	60–64	155.9	255.9	1.64	1.56–1.73	< 0.001
	65–69	173.3	297.4	1.72	1.63–1.80	< 0.001
	70–74	176.7	231.5	1.31	1.23–1.39	< 0.001
	75–79	195.9	219.3	1.12	1.05–1.20	0.002
	80–84	193.0	269.1	1.39	1.29–1.50	< 0.001
	85+	224.6	364.3	1.62	1.52–1.73	< 0.001
	Total	179.4	267.7	1.49	1.46–1.53	< 0.001
ED presentations ^e	60–64	61.6	74.0	1.20	1.10–1.31	< 0.001
	65–69	70.5	88.2	1.25	1.15–1.36	< 0.001
	70–74	86.8	76.5	0.88	0.80–0.97	0.007
	75–79	104.2	80.9	0.78	0.70–0.86	< 0.001
	80–84	114.3	109.6	0.96	0.86–1.07	0.432
	85+	124.3	126.9	1.02	0.93–1.13	0.677
	Total	85.2	87.3	1.02	0.99–1.06	0.204
Hospitalisations	60–64	16.6	19.5	1.18	1.00–1.39	0.046
	65–69	25.4	28.1	1.11	0.96–1.28	0.160
	70–74	35.5	29.3	0.83	0.71–0.95	0.009
	75–79	54.6	45.5	0.83	0.73–0.95	0.008
	80–84	90.9	75.5	0.83	0.73–0.94	0.003
	85+	132.9	158.9	1.20	1.09–1.31	< 0.001
	Total	46.0	46.1	1.00	0.95–1.06	0.900

a Rate per 100,000 person-years.

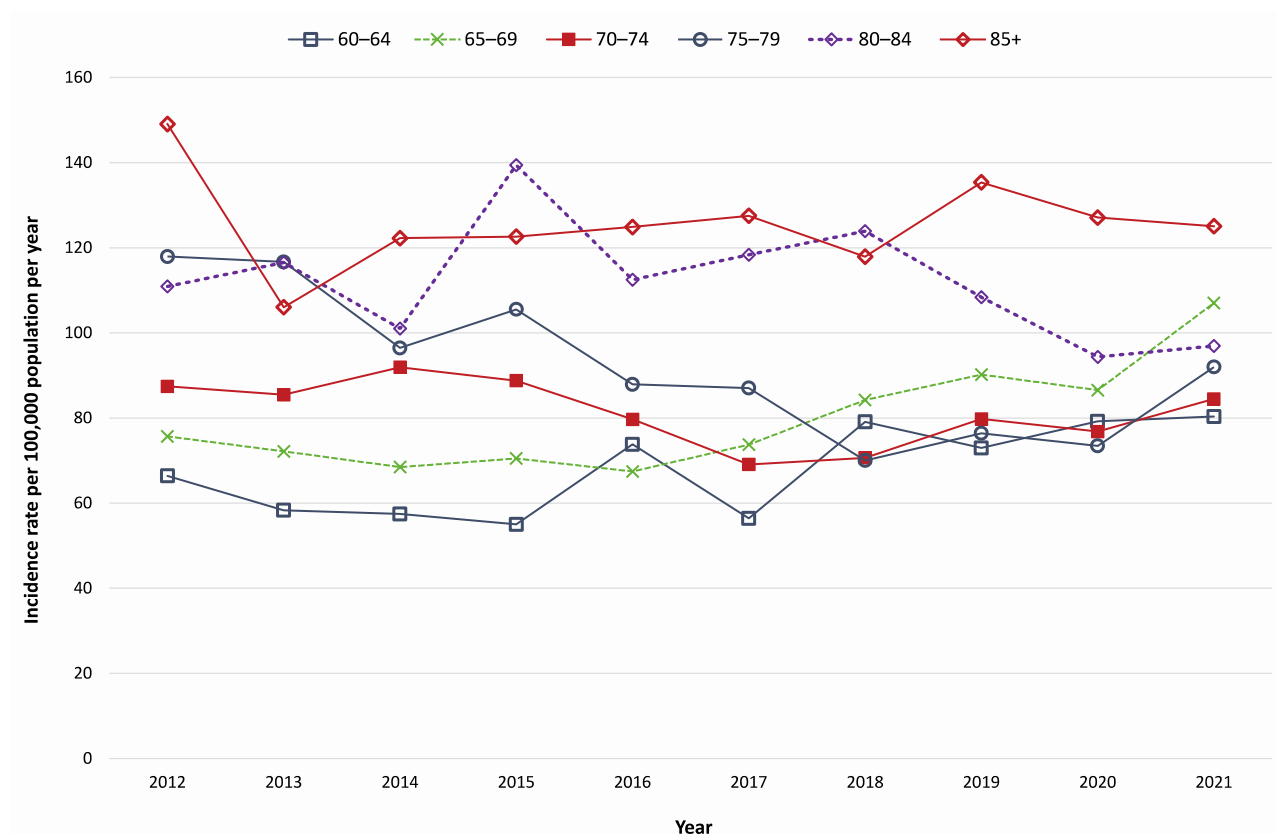
b Pre-NSVP: pre-implementation of the National Shingles Vaccination Program (NSVP), 1 January 2012 to 31 October 2016; Post-NSVP: post-implementation of the NSVP, 1 November 2016 to 31 December 2021.

c IRR: incidence rate ratio.

d 95% CI: 95% confidence interval.

e ED: emergency department.

Figure 4: Age-specific rates of emergency department presentations due to HZ aged 60 years and over by five-year age groups, Victoria, Australia 2012–2021



Hospitalisations

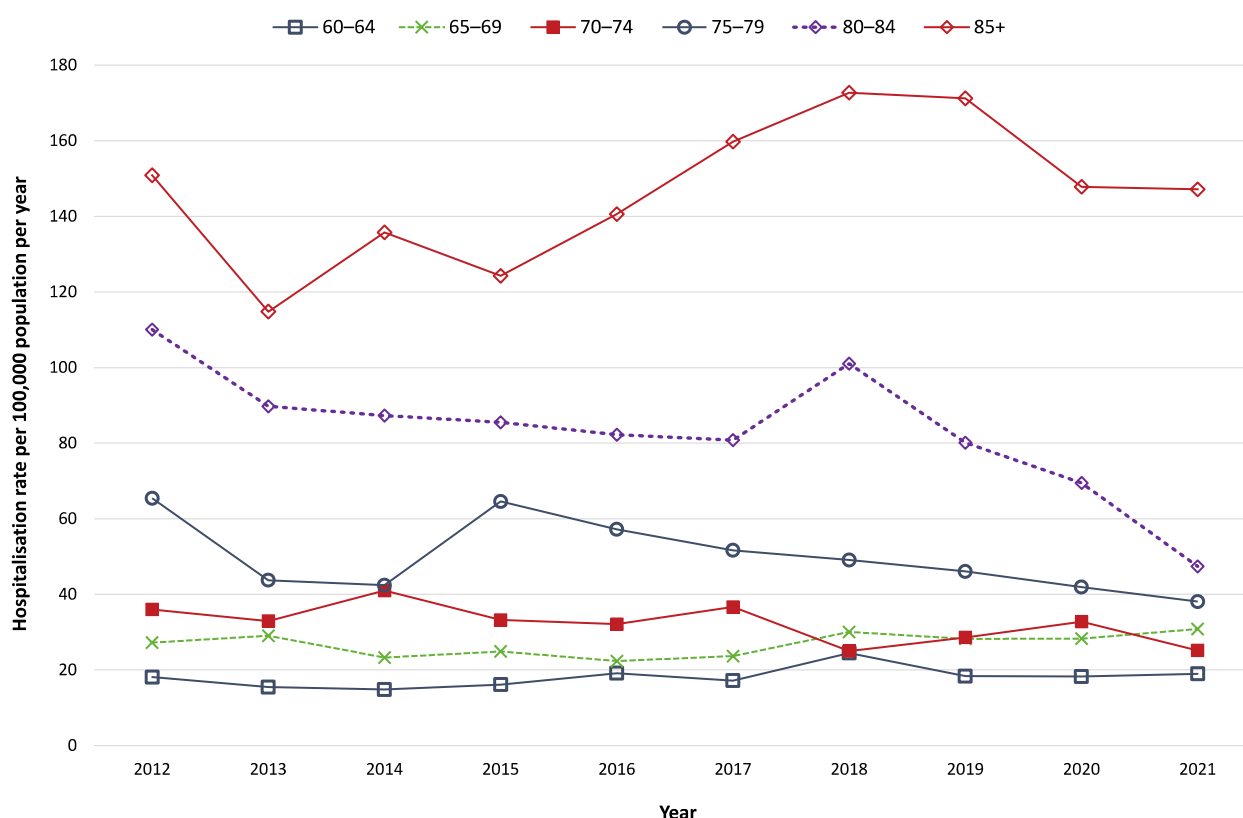
There were 15,797 HZ-related hospitalisations recorded, of which 5,872 (37.2%) were coded as hospitalised due to HZ (primary illness) (Table 1). Among those hospitalised due to HZ, the median length of stay was 4 days (IQR: 1–9 days), and 66 (1.1%) required intensive care unit admission. Females had a slightly higher age-standardised hospitalisation rate (HR) than males, with respectively 48.3 and 40.6 hospitalisations per 100,000 population over the study period.

For those with a HZ-primary illness, crude HRs remained relatively stable (Table 2). From 2012 to 2021, age-specific HRs declined for the age groups 70–74, 75–79, and 80–84 years, but increased and remained highest among those aged 85+ years (Figure 5). IRRs comparing pre-NSVP to post-NSVP showed a statistically significant decline in hospitalisations for the 70–74, 75–79, and 80–84 years age groups, but a statistically significant increase for the 60–64 and 85+ years age groups (Table 4).

Deaths

A total of 341 death certificates indicated a HZ-related cause-of-death, with 189 (55.4%) listing a HZ-related primary cause. Most deaths occurred in the 85+ years age group and the majority were female (Table 1). The crude mortality rate associated with HZ declined between 2012 and 2021 (Table 2). The age-specific mortality rate for adults 85+ years declined from 12.1 (pre-NSVP) to 8.1 (post-NSVP) per 100,000 person-years.

Figure 5: Age-specific rates of hospitalisations due to HZ aged 60 years and over by five-year age groups, Victoria, Australia 2012–2021



Discussion

We hypothesised that cases, ED presentations, hospitalisations and deaths would all decline following NSVP implementation. However, we found that HZ continues to cause significant disease among those aged ≥ 60 years. Vaccination uptake remains low, and is substantially lower among those for whom vaccination is recommended but who are not eligible for NIP-funded vaccine. Further work is needed to improve vaccination rates to reduce the burden of HZ in Victoria.

Whilst NIRs initially declined amongst the NIP-eligible population as described in the literature,^{10,12,13} these gains have not been sustained. This may be associated with waning vaccine effectiveness.^{10,12,13} However, previously published incidence rates of HZ are higher than we observed,^{1,3} suggesting under-ascertainment of cases in our study. Individuals experiencing HZ may not present to healthcare settings or may not be tested for HZ. Although varicella is a

notifiable condition in Victoria, the majority of notifications (72.6%) were for varicella unspecified, suggesting there may be underreporting of cases by medical practitioners. Testing data suggests that the increasing NIRs we observed may be associated with increased testing, and consequently higher case ascertainment over time, particularly as there is a reliance on notifications through laboratories rather than through clinical channels. Changes in case ascertainment may impact the use of notification data to accurately evaluate the NSVP and other HZ-related interventions.

Other investigations of the NSVP have used data sources such as antiviral prescription^{10,16} and general practice data^{12,13} as proxies for disease incidence. Each of these approaches has strengths and limitations, with notification data capturing a wider range of health settings but likely providing an underestimate due to underreporting and a reliance on laboratory

notifications. Using a combination of datasets would better support our understanding of the impact of the NSVP on disease incidence.

As the NSVP aims to reduce the severe complications of HZ, ED presentation and hospitalisation rates are important for assessing impact. Our study found that rates for both hospitalisation and ED presentations have fallen among the NIP-eligible (70–79 years) and 80–84 years age groups, who were NIP-ineligible at the time of diagnosis, but may have potentially been vaccinated when they were in the NIP-eligible age groups. This suggests the NSVP has contributed to a decline in severe complications among these age groups. However, annual hospitalisation rates demonstrate that this decline commenced prior to the NSVP when vaccination uptake remained very low, suggesting factors other than the NSVP may have also contributed to this decline. In contrast, ED presentation and hospitalisation rates have risen among the younger (60–69 years) and older (85+ years) age groups. Further work is needed to investigate reasons for both lower vaccination uptake and increased ED and hospitalisation rates within these groups.

We found that the older age groups (80+ years), who are not eligible for NIP-funded HZ vaccination, had both the highest hospitalisation and highest death rates due to HZ. Death rates fell between the pre-NSVP and post-NSVP periods, with the greatest decline seen amongst those aged 85+ years. However, as vaccination uptake among this age group was very low,²² this decline may be due to factors unrelated to the NSVP. The data suggest that while the number of deaths where HZ was listed as the primary cause decreased over the study period, the number of deaths where HZ was listed as an antecedent cause increased. Death due to HZ is rare,²² and it is possible the rates observed were overestimated due to HZ being misclassified as a primary cause of death rather than an antecedent condition contributing to death.

Improving vaccination rates in the target population should ideally lead to reduced levels

of HZ disease, hospitalisations, and deaths. Several factors may be contributing to poor vaccination uptake; however, the cost associated with vaccination in the NIP-ineligible age groups is likely a key barrier. Targeted interventions^{11,14} to increase vaccination uptake across all recommended age groups and consideration of expanding funded vaccine eligibility criteria are likely to be required into the future.

In the initial six months following introduction of Shingrix to the private market, there was reasonable uptake among the NIP-ineligible Victorian populations despite the greater cost involved, with around half of younger age groups (60–69 years) utilising Shingrix rather than Zostavax. However, this was not consistent across the entire study population, with the overall uptake of Shingrix vaccination remaining low. With the Australian Government recently announcing Shingrix would replace Zostavax on the NIP,⁸ further investigation is required to understand how this will affect vaccination uptake, particularly given immunocompromised adults aged ≥ 18 years are recommended to receive Shingrix.³ Furthermore, with most individuals only receiving a first dose during the study period, there is a need to reinforce the importance of completing vaccinations within the recommended timeframe.

The COVID-19 pandemic may have influenced 2020 and 2021 data. Emerging evidence suggests that COVID-19 infection increases the risk of developing HZ, which may have led to increases in notification, ED presentation and hospitalisation rates.²³ However, cases may alternatively have been less likely to present for mild infections due to restricted access and availability of medical care, as observed among other populations.²⁴ Our results and prior research show a slight decline in VRs in 2020,^{24–26} which may be associated with deferred vaccinations or COVID-19 related vaccine hesitancy.²⁵ As mandatory reporting of all NIP-listed vaccines only took effect from 1 July 2021, it is difficult to ascertain what factors influenced vaccination uptake for HZ prior to the pandemic.

This study utilised routinely collected surveillance data, with several limitations. Though unlikely, some varicella zoster ‘unspecified’ cases may have been chickenpox, leading to an overcount of cases. As discussed, there are limitations in interpreting the notification and testing data. In particular, testing data were limited by gaps in laboratory records and by the use of multiplex testing, as some tests were conducted for other illnesses, and age analyses were not available. Changes to coding and reporting over time can impact on administrative datasets, for example hospitalisation rates in 2012 and 2013 may have been underreported as mandatory reporting for all conditions from both public and private hospitals only came into effect from September 2013.²⁷ The use of ERPs to calculate annual vaccination rates poses limitations, as individuals previously vaccinated are included in the total estimated population, even when they are not recommended for additional vaccinations, and the population may change due to immigration and emigration from Victoria. Mandatory reporting to the AIR for all NIP vaccines only commenced in July 2021. The data suggests that, consistent with prior research,²⁸ a substantial undercount of vaccinations likely occurred during the early years of the NSVP (i.e. 2016 and 2017). The introduction of mandatory reporting may be associated with the slight increase in VRs observed in 2021, and will likely enable more accurate analysis of AIR data in the coming years.

Despite these limitations, this analysis furthers our understanding of the possible impacts the NSVP has had on the epidemiology of HZ. Whilst this study focussed on Victoria, the NSVP is a national vaccination program and the results may be generalizable to other Australian states and territories. Our results suggest the NSVP may have led to a decline in severe complications of HZ amongst those eligible for funded vaccination. However, the burden of this disease may be increasing among those age groups recommended to be vaccinated but ineligible for NIP-funded vaccines. It will be important to increase vaccination coverage across all target populations to further reduce the burden

of HZ in Victoria. The addition of Shingrix to the NIP is an important step, given evidence suggests it is both more effective and provides longer protection.³ Although the age groups recommended for HZ vaccination have recently been expanded,³ eligibility for funded vaccination remains limited. Our results suggest the burden of disease is unlikely to decrease unless vaccination coverage increases. Consideration should be given to expanding the age groups eligible for NIP-funded HZ vaccination. Future evaluations need to be planned and implemented at a national level to better understand the impact of expanding NIP eligibility and to inform future decisions around funding for HZ vaccination. These evaluations would benefit from investigating HZ using linked datasets to analyse the role of vaccine effectiveness and its impacts on HZ epidemiology.

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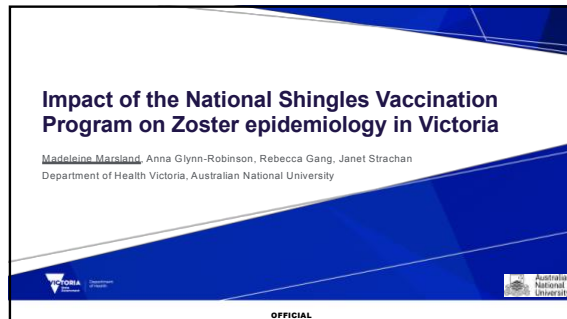
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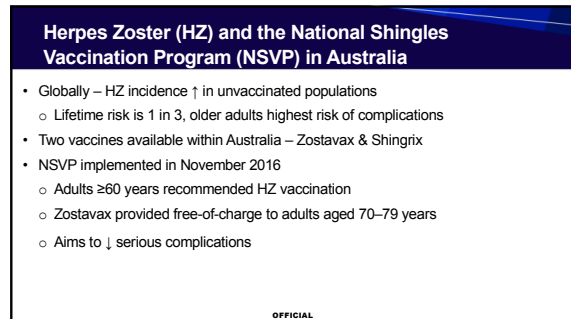
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APPENDIX A: CONFERENCE PRESENTATIONS

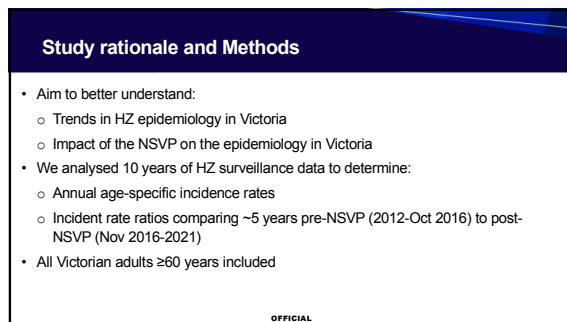
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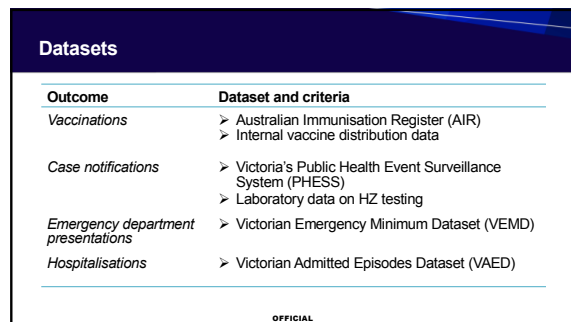
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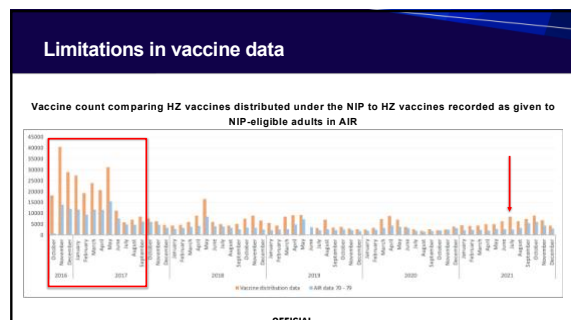
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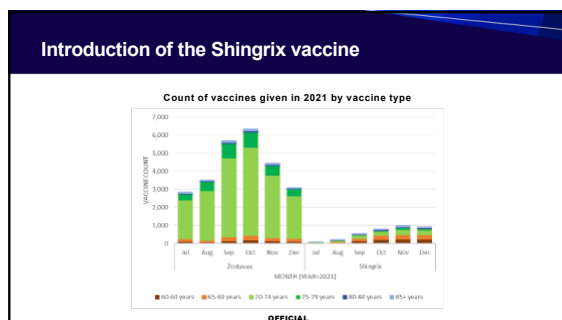
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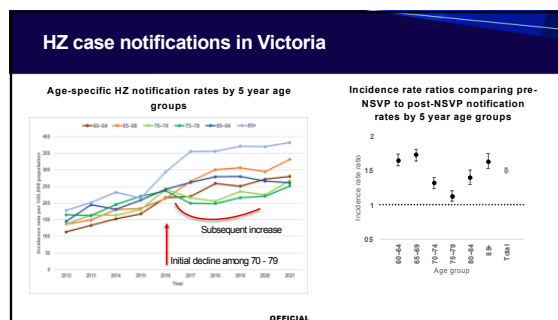
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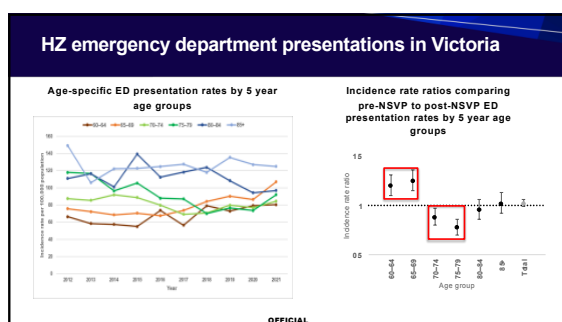
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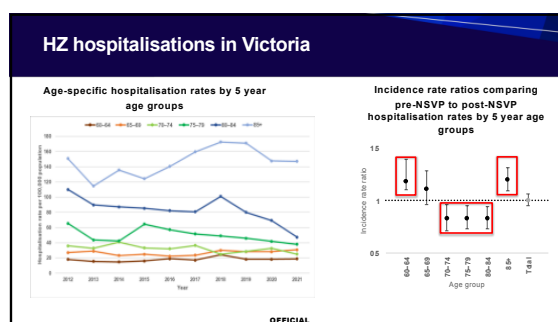
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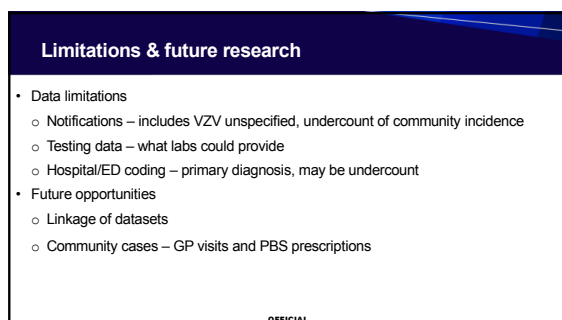
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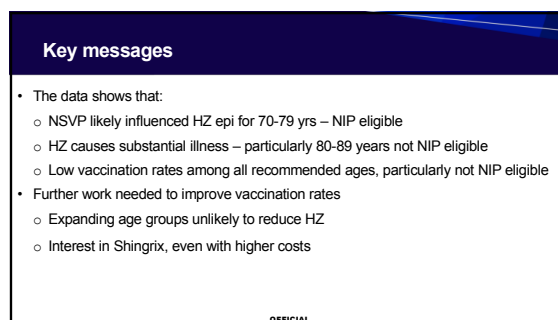
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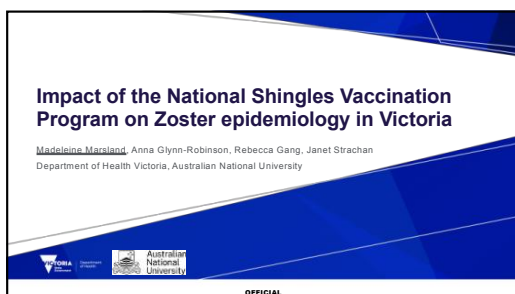


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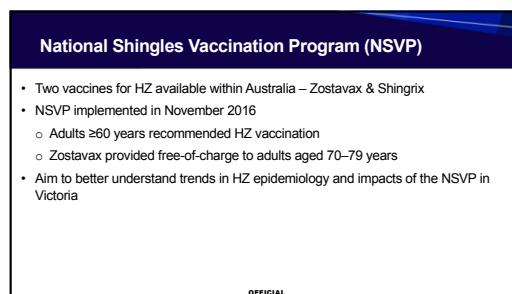


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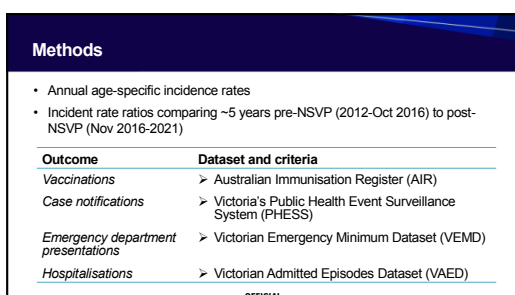
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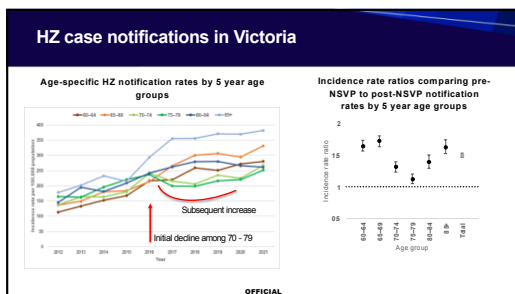
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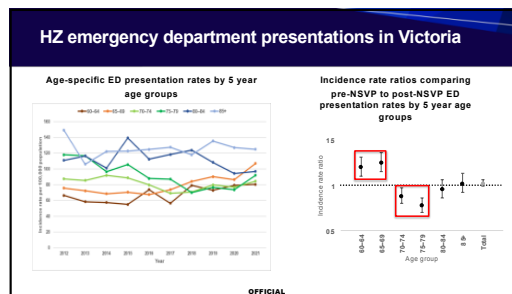
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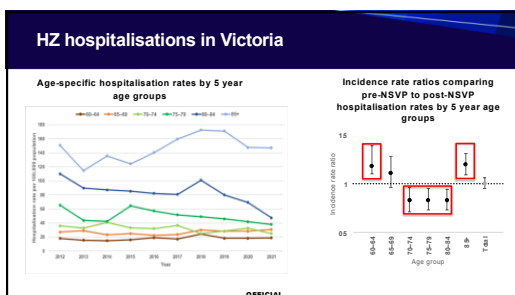
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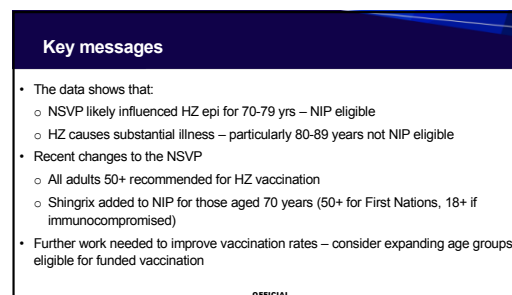
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CHAPTER III

EPIDEMIOLOGICAL STUDY

Japanese encephalitis serosurvey following an outbreak in an immunologically naïve region in Victoria, Australia

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PROLOGUE

Study rationale

In March 2022, the first locally-acquired cases of Japanese encephalitis (JE) were reported in south-eastern Australia. The population was largely immunologically naïve, and with limited vaccine supply, there was an urgent need to better understand the distribution of infection and risk factors for infection, to inform public health planning. Within this context, this serosurvey was conducted in northern Victoria across a region thought to be at highest risk of Japanese encephalitis virus (JEV) infection. This MAE project focussed on risk factors associated with JEV infection, with the aim of informing vaccination and prevention strategies, such as vaccine prioritisation and public messaging. Another MAE scholar, Tilda Thomson, considered the geographical distribution of infection to address the other core aims of this study.

My role

I co-lead this study along with Tilda Thomson. Together we collaboratively led the design, management, analysis and write-up for this study. In the interest of demonstrating how this met our MAE competencies, a comprehensive summary of our roles and responsibilities is provided at Appendix A. We conducted a literature review prior to commencing the project (Appendix B). I also produced several lay summaries for this project, including information sheets for participants (Appendix C) and a summary of the high-level results which was disseminated to participants and published on the DH website (Appendix D).

Tilda and I coordinated stakeholders and oversaw all associated work. The National Centre for Immunisation Research and Surveillance (NCIRS) provided national coordination and supported our ethics application and associated amendments. Relevant local public health units (LPHUs) contributed to the design and implementation of the study supporting advertising, recruitment and follow-up of participants in their respective regions. The Victorian Infectious Diseases Reference Laboratory (VIDRL) provided laboratory expertise and conducted testing, which included coordinating additional testing through the Institute of Clinical Pathology and Medical Research (ICPMR). Other staff members from the Department of Health (DH) supported budgeting, governance arrangements, and assisted Tilda and me to develop the protocol and work through some of the problems that arose during the course of the study. Representatives from VIDRL and DH contributed to the Expert Review Panel (ERP).

Lessons learned

This project was a significant undertaking and required leadership, coordination and problem solving, working within a budget, and managing a broad range of stakeholders. Public health

is a team sport, and it was valuable to work in close partnership with Tilda, harnessing our different skill sets and supporting each other's development through our respective strengths.

There were many lessons learned through designing the study protocol. Many stakeholders were involved in early discussions on concept and design, which resulted in the scope of the project expanding. This posed challenges for coordinating the project, with some of the implications of this expansion not identified until after recruitment commenced. An early problem we faced involved mismatches between laboratory results and questionnaire data indicating that some recruitment sites were not following the project's protocols. This had implications for data quality and ethics. We were able to rectify this issue, however this showed me the importance of having strong protocols with easy-to-follow instructions for participants, pre-briefing all team members involved in each stage of a project, and identifying issues early to find solutions. From this experience I have learned the importance of taking the time for planning even in high stress environments where there is pressure to move quickly.

We developed a recruitment target based on sample size calculations and budget. However, midway through the project some of our geographical areas were having greater success in recruitment than others. The LPHUs struggling with recruitment reached out to us to raise concerns and present proposed solutions. We progressed these by opening additional recruitment sites, increasing advertising and extending the duration of recruitment. While these mitigation strategies were put in place, in some regions recruitment remained low due to extensive flooding occurring in the later stages of recruitment, which was an unfortunate limitation of the study. From this, I learned the importance of having contingency plans in place from the outset of a project and, again, the benefits of spending additional time on program planning. This also showed the importance of trusting local stakeholders and people on the ground when they raise issues, and taking pre-emptive action when problems arise.

Our biggest challenge occurred late in recruitment. Our ethics application had been done as an amendment to the national protocol. Late in the study it became apparent that there had been an oversight and the 'Victorian Specific Module', a legislative requirement, had not been completed. We were able to address this within hours by seeking an urgent ethics amendment. However, through this process, one of the LPHUs initially involved in the project identified some broader governance concerns and subsequently withdrew from participating in the study and we were required to absorb the additional work into our day-to-day responsibilities. These concerns reflected ongoing uncertainty regarding the newly formed DH and LPHU working relationship. Some of these issues were beyond the scope of the project and so it was important for us to recognise what we could resolve and what was out of our control.

The serological testing also posed some challenges, with the testing assays still being refined and some results being ambiguous and difficult to interpret. This resulted in some participants requiring re-bleeds, which delayed the final results and also led to some loss to follow-up. VIDRL had suggested establishing an ERP to finalise results, and we had initially questioned the need for this. However, this experience showed the clear benefit of having multi-disciplinary teams and laboratory expertise involved in the decision-making.

As we started releasing positive results, we worked with stakeholders to refine our follow-up questions. Some of our early results included two positive individuals from a household. From this very initial finding stakeholders suggested that household members should receive testing. We realised that this could be an interesting sub-analysis of the study, with obvious public health implications for household members of future JE cases. We were able to adjust the protocol and ethics to accommodate this change. This showed me the value of listening to all ideas and being flexible to change existing plans when new ideas were raised.

Public health implications

The evidence from this project supported a greater understanding of risk factors associated with JEV infection among immunologically naïve populations. This informed prevention strategies in Victoria, including the expansion of vaccine eligibility criteria throughout late 2022 and early 2023. The results also supported the broader national serosurveillance program, informing national public health prevention and vaccination strategies. The results may have international implications, with the potential for JEV to move into new regions in the future.

The literature review was published in the [Australian and New Zealand Journal of Public Health](#) (see Appendix B) and we were also approached to develop a follow-up article for [InSight+](#) the Medical Journal of Australia's medical news publication (Appendix E). A lay summary of results from the JEV serosurvey was published on the [DH website](#) (Appendix D) and was widely disseminated within news and media. A manuscript of the final results has been accepted for publication in the Medical Journal of Australia, the final version is reproduced in full (Appendix F). I presented the components of the study relating to my MAE project at the Communicable Diseases & Immunisation Conference 2023 and at the SAFETYNET conference 2023 (Appendix G). Results were also presented in a range of other internal and external fora and meetings. Along with two other MAE scholars, Tilda Thomson and Zoe Baldwin, I wrote a case study of our involvement in the Australian JE serosurveillance program for the [TEPHINET annual report](#). Tilda and I also developed a presentation that formed part of the online content for Monash University's Master of Public Health degree.

This study also informed further research into flaviviruses in Victoria. In early 2023, planning commenced on a Murray Valley encephalitis (MVE) serosurvey in northern Victoria, which was led by a first year MAE scholar, Marie Heloury. I was part of the study team and provided support for the design and management of the study, including applying lessons from the JEV serosurvey. Residual samples from the JEV serosurvey were tested for MVE and Kunjin and Tilda and I conducted a preliminary analysis to inform the MVE serosurvey. High level results were included in the JE serosurvey manuscript that was accepted for publication in the Medical Journal of Australia (Appendix F).

Acknowledgements

This project was a major challenge for me and a highlight of the MAE program, it would not have been possible without the support of many others. First and foremost, I acknowledge my teammate and work-wife Tilda, I have learned so much from working with her but more than anything have valued having someone to bounce my ideas off, split the day-to-day chores with, and share in the victories and defeats of the study.

I would also like to acknowledge the leadership of Deb Friedman and Helen O'Brien, whose guidance and support were instrumental to this project. I am grateful for their faith in us and for always being available as our day-to-day supervisors to answer questions and help us have confidence in our approach. I also acknowledge Kathryn Snow, Corinna Minko and Jim Black who supported us to take on this study as an MAE project and provided instrumental guidance during the early stages of protocol design.

As with all of my projects, my MAE supervisors Janet Strachan, Rebecca Gang and Anna Glynn-Robinson provided invaluable support. I am especially grateful for their trust in allowing Tilda and me to be the drivers of this project, particularly as JE was outside the initial scope of my MAE placement, and supporting me to work to the tight timeframes of this project even though at times it impacted my other responsibilities.

Finally, I would like to acknowledge the many partners involved in the project from NCIRS, VIDRL, the LPHUs, and the pathology providers. I am grateful for everyone's support as we took on this major project, for being willing to answer my questions and help me learn, and for their understanding when things did not go to plan. This was an incredible learning experience and that comes down to the willingness of everyone to accommodate myself and Tilda. It has been a pleasure to work with all of our partners.

ABSTRACT

Introduction

In early 2022, the first locally-acquired cases of Japanese encephalitis were reported in Victoria. Most infections of Japanese encephalitis virus (JEV) are asymptomatic, and the true burden of infections remains uncertain in the Australian context. There is limited evidence regarding risk factors for JEV infection in immunologically naïve populations, with most available evidence from endemic regions. This study sought to investigate demographic, behavioural risk and protective factors for JEV infection to guide vaccination and preparedness strategies.

Methods

A cross-sectional serosurvey was conducted in northern Victoria between August and December 2022. Asymptomatic participants were recruited during routine blood tests (opportunistic), through community outreach and advertising (targeted), or after a household member tested seropositive in the study (household). All participants completed a study specific questionnaire and serological testing to determine if they had evidence of prior JEV infection. Results were descriptively analysed and prevalence odds ratios (PORs) were calculated for investigated exposures. Household recruits were excluded from the primary analysis, and a household-member sub-analysis was conducted.

Results

In the primary analysis, 27 of 813 (3.3%) participants displayed evidence of prior JEV infection. Older age ($p<0.01$) and contact with feral pigs ($p=0.01$) were found to be significantly associated with JEV infection. The sample was skewed towards being female (61.0%), and although sex was not statistically associated ($p>0.05$), more seropositive individuals were male (51.9%). Of the 27 seropositive participants, two groups were couples ($n=4$). Other than these couples, no additional household recruits were seropositive.

Discussion

A substantial proportion of the northern Victoria population may have had JEV infection during the 2022 outbreak; however, there remains widespread population vulnerability to future infection. Few investigated exposures were statistically associated with prior JEV infection, demonstrating the difficulty of developing evidence-based vaccine eligibility criteria. Further research will be required to investigate other potential risk factors such as being male and shared risk of exposures among household members of seropositive persons. Given these findings, a population wide vaccination strategy may be needed to reduce future infections.

INTRODUCTION

Japanese encephalitis virus (JEV) is a zoonotic flavivirus that is primarily transmitted via *Culex* mosquitoes [1-3]. Pigs are the central amplifying hosts of this virus, and migratory birds are important maintenance hosts [1, 2, 4, 5], with humans and horses both being dead-end hosts [4, 6]. The majority of JEV infections are asymptomatic, with approximately 0.1% to 1% of infections resulting in Japanese encephalitis (JE) [3, 7-9], and up to 10% experiencing mild clinical illness [10]. In immunologically naïve populations, the ratio of subclinical to clinical infections may be higher than in endemic populations, with estimates ranging from 1 in 25 to 1 in 300 [11-15].

Of all flaviviruses, JEV is notable for causing significant morbidity and mortality, with disability-adjusted life years for this virus indicating a greater burden of disease compared with other arthropod-borne viruses [6, 7]. The case fatality rate is approximately between 20% and 30% of clinical infections [3, 9]. A further 30% to 50% of JE cases experience sequelae [3, 9, 16], which range from persistent motor deficits to severe cognitive and language impairments [4].

In endemic countries, the most significant risk factor associated with JEV infection is age, with children being at greatest risk as they are more likely to be immunologically naïve [1, 3, 17]. Other factors that are thought to increase the risk of JEV infection primarily relate to mosquito exposure, with rural areas and residential proximity to common breeding grounds for mosquitoes, such as rice fields, lakes or ponds, all shown to likely increase the risk of infection [5, 8, 16-20]. Some evidence has also shown work and social factors may also impact risk, for example patterns of work attendance and proximity to piggeries [2, 5, 8, 12, 17, 20].

As there is currently no effective treatment available for JE [1, 7], preventing infection through effective vaccination and mosquito control programs is essential [1, 21]. Whilst vaccination cannot produce herd immunity, it can reduce transmission intensity and is the most effective method of control [4, 6]. Two JEV vaccines are licensed within Australia – Imojev, a live recombinant vaccine, and JEspect, an inactivated vaccine [22-24]. Prior infection with JEV is also thought to provide lifelong immunity.

A variety of host, virus and environmental factors can lead to flaviviruses spreading into new regions, such as wind-blown mosquitoes, bird migration, or movement of infected animals and people [4]. Prior to 2022, a total of 6 locally-acquired cases had been reported in Australia and the southerly limit of disease was in the far north of Australia [23, 25]. In early 2022, JEV was detected in humans, pigs and mosquitoes across New South Wales (NSW), Victoria, Queensland and South Australia [24, 26].

The outbreak was the first time locally-acquired JEV had been reported in south-eastern Australia [23, 24]. Given the subclinical to clinical ratio, it is thought that thousands of JEV infections have likely occurred nationally [23, 25]. JEV vaccination is not offered through the National Immunisation Program (NIP) [22]. During the initial outbreak, Australia prioritised select groups for vaccination, including individuals who work or reside near piggeries and pork abattoirs, but this was expanded in the latter half of 2022 to include adults over the age of 50 years who spent four hours or more outdoors daily, and later to all age groups in risk areas [26]. However, for vaccination programs to be truly effective, further changes may be required to target the wider population [23, 27, 28].

This study aimed to investigate the seroprevalence of JEV in northern Victoria following the initial outbreak to identify factors that may increase the risk of infection. This work was intended to inform local vaccination and prevention programs ahead of future mosquito seasons.

METHODS

A cross-sectional serosurvey was conducted in northern Victoria across a region considered to be at risk of JEV infection based on 2022 outbreak data (e.g., mosquito detections, infected piggeries, and exposures for human JE cases). Participants were invited to participate if they met the eligibility criteria (Table 1). Individuals who had been previously vaccinated were excluded as serology testing cannot determine a difference between an exposure and JEV vaccination.

A multimodal recruitment strategy was used to engage participants:

1. Opportunistic: participants who were recruited whilst routinely having blood taken at a participating pathology site;
2. Targeted: community outreach and advertisement to encourage members of the community to participate, particularly those who were expected to be underrepresented in opportunistic recruitment (e.g. younger males who are less likely to attend for routine blood collections); and
3. Household: household members of participants who tested seropositive were invited to participate.

Table 1: Participant eligibility criteria

Inclusion criteria	Exclusion criteria
- Lives, works or visits a recruitment location in one of three Local Public Health Unit catchment areas in northern Victoria: Ovens Murray; Goulburn Valley; or Loddon Mallee. - Completes the online questionnaire and has a blood sample taken.	- Has received a vaccine for JE. - Has previously been diagnosed with JE. - Born in a country where JEV is endemic (Bangladesh, Brunei, Burma, Cambodia, China, Guam, India, Indonesia, Japan, Laos, Malaysia, Nepal, North Korea, Pakistan, Papua New Guinea, Philippines, Russia, Saipan, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, Timor-Leste, Vietnam).

Recruitment occurred from August to December 2022. Participants were provided with an information sheet and completed informed consent via an online form, with parent or guardian consent required for those under 18 years. All participants completed a study specific questionnaire to collect information on demographic, risk and protective factors. The questionnaire was designed based on prior literature and internal data on risk factors that were identified from JE cases during the 2022 outbreak. Upon completing the consent form and questionnaire, participants had a blood sample collected for serological testing.

All participants were tested for JEV IgM and IgG antibodies at the Victorian Infectious Diseases Reference Laboratory (VIDRL). Positive samples were sent for confirmatory testing at the Institute of Clinical Pathology and Medical Research (ICPMR) in NSW. Testing for seropositive samples occurred across four JEV serology assays, details on the testing algorithm have been published elsewhere [29]. Additional testing was also conducted for other flaviviruses (Dengue virus, Murray Valley encephalitis virus and Kunjin virus) to assess for cross-reactivity. Final results were determined by an Expert Review Panel (ERP), with participants classed as 'seropositive' if they had evidence of prior JEV infection (i.e. IgG positive and total antibody positive) and 'seronegative' if there was insufficient evidence to suggest prior JEV infection. Participants received a telephone call requesting additional testing be conducted (a re-bleed) if requested by the ERP to support interpretation of results, provided they still did not meet the eligibility exclusion criteria (Table 1).

All participants were notified of their results and provided with an information sheet (Appendix C). Participants who were seropositive were invited to complete a follow-up telephone interview to clarify answers from their questionnaire responses, and to invite household members not already involved in the study to participate.

The data were separated into a primary analysis and a household-member sub-analysis. Analyses were undertaken using Stata version 16 [30].

The primary analysis (general population) included all participants recruited through opportunistic or targeted recruitment. If more than one household member was involved in the study, the first person in a household who tested seropositive was considered a 'principal' case. Participants recruited through households after a principal case was identified (household recruits) were excluded from the primary analysis to minimise the risk of selection bias.

A sub-analysis (household members) was conducted to investigate whether being a household member of a JEV seropositive person was associated with JEV infection. Participants were included in this sub-analysis if they shared a residential address with a principal case. Principal cases were excluded from the sub-analysis. Participants who were recruited within household groups through opportunistic or targeted methods (i.e., before a household member tested seropositive) were included in both the primary and sub-analyses.

Results were descriptively analysed, with medians and ranges presented. Prevalence odds ratios (PORs) were calculated and p-values derived using the Fishers exact test for categorical variables, and logistic regression for continuous variables. Confidence intervals were derived assuming a binomial distribution.

Ethics approval was received from the Sydney Children's Hospital Network Human Research Ethics Committee (protocol 2022/ETH01167).

RESULTS

A total of 818 eligible participants were recruited. Of these, 660 (80.7%) were recruited opportunistically, 153 (18.7%) using targeted methods, and five (0.6%) as household members of a JEV seropositive participant. After excluding household recruits, a total of 813 participants were included in the primary analysis. Four of these individuals were included in both the primary and household sub-analyses (i.e. household members recruited opportunistically or through targeted methods) and an additional five were included in the sub-analysis only (household recruits). Of the 27 participants who tested seropositive, 23 (85.2%) completed a follow-up questionnaire.

No samples suggested recent infection (i.e. confirmed IgM positive). Based on the initial results, the ERP requested 14 (1.7%) participants have re-bleeds. Of these, six re-bleeds were completed all of whom were seronegative. Eight rebleeds were not completed; five due to the participant having received a JEV vaccine since their initial test; and three due to loss to follow-up. The ERP classified all participants as seronegative based on their initial results.

Primary analysis (general population)

In the primary analysis, 27 of 813 (3.3%) participants had evidence of prior JEV infection. Of those recruited opportunistically 3.0% (20/660) were seropositive compared to 4.6% (7/153) of those recruited through targeted methods. This difference was not statistically significant ($p=0.321$).

Demographics

Demographics of participants are reported at Table 2. Of those who tested seropositive, all were born in Australia, and most (59.3%) had never travelled to an endemic country. Six of 23 seropositive participants (26.1%) who completed the follow-up interview reported previous travel to an endemic region for a period greater than one month.

Table 2: Demographics of participants in primary analysis

Demographic factors	JEV positive, no. (%)	JEV negative, no. (%)	Total participants, no. (%)
Age Group (years)			
0-9	0 (0.0)	1 (100.0)	1 (100.0)
10-19	0 (0.0)	21 (100.0)	21 (100.0)
20-29	1 (1.6)	63 (98.4)	64 (100.0)
30-39	1 (1.0)	103 (99.0)	104 (100.0)
40-49	0 (0.0)	90 (100.0)	90 (100.0)
50-59	3 (2.2)	131 (97.8)	134 (100.0)
60-69	5 (2.5)	197 (97.5)	202 (100.0)
70-79	11 (7.3)	140 (92.7)	151 (100.0)
80+	6 (13.0)	40 (87.0)	46 (100.0)
Sex			
Male	14 (4.4)	303 (95.6)	317 (100.0)
Female	13 (2.6)	483 (97.4)	496 (100.0)
Aboriginal and Torres strait islander descent			
Not Aboriginal or Torres Strait Islander	25 (3.2)	757 (96.8)	782 (100.0)
Aboriginal	1 (7.7)	12 (92.3)	13 (100.0)
Torres Strait Islander	0 (0.0)	1 (100.0)	1 (100.0)
Prefer not to say	1 (5.9)	16 (94.1)	17 (100.0)
Country of birth			
Australia	27 (3.6)	713 (96.4)	740 (100.0)
Other non-endemic country	0 (0.0)	73 (100.0)	73 (100.0)
Total	27 (3.3)	786 (96.7)	813 (100.0)

The median age of participants was 59 years (range 7 to 92 years) and the median age of seropositive participants was 73 years (range 25 to 90 years). Only 16 participants were children (<18 years), none of whom tested seropositive. PORs showed a statistically significant association between age and JEV infection, with the odds of infection increasing

by 1.07 per year of age ($p < 0.001$), and seropositive participants more likely to be aged 50+ years (POR 6.84, $p = 0.002$ compared with those aged <50 years).

Although the majority of participants were female (61.0%), approximately half (51.9%) of seropositive participants were male (POR 1.72). However this was not statistically significant ($p > 0.05$). When considering age and sex, males over the age of 60 years comprised 51.9% of all seropositive participants (Table 3).

One seropositive participant identified as Aboriginal. However, the overall sample identifying as Aboriginal ($n = 13$) or Torres Strait Islander ($n = 1$) was low.

Table 3: Age and sex of participants in primary analysis

Age	Male				Female			
	JEV positive, no.	Total, no.	JEV positive, %	95% CI, %	JEV positive, no.	Total, no.	JEV positive, %	95% CI, %
0–9	0	1	0.0	0.0–97.5	0	0	-	-
10–19	0	7	0.0	0.0–41.0	0	14	0.0	0.0–23.2
20–29	0	11	0.0	0.0–28.5	1	53	1.9	0.0–10.1
30–39	0	24	0.0	0.0–14.2	1	80	1.3	0.0–6.8
40–49	0	35	0.0	0.0–10.0	0	55	0.0	0.0–6.5
50–59	0	51	0.0	0.0–7.0	3	83	3.6	0.8–10.2
60–69	3	86	3.5	0.7–9.9	2	116	1.7	0.2–6.1
70–79	7	80	8.8	3.6–17.2	4	71	5.6	1.6–13.8
80+	4	22	18.2	5.2–40.3	2	24	8.3	1.0–27.0
Total	14	317	4.4	2.4–7.3	13	496	2.6	1.4–4.4

Investigated exposures

Among seropositive participants, the most common occupation was farming (4/27, 14.8%), with approximately half reporting being retired (13/27, 48.1%). None of the investigated occupations were found to be significantly associated with JEV infection ($p > 0.05$) (Table 4).

Table 4: Univariable prevalence odds ratios of risk and protective factors

Exposure variable	JEV positive, no. (%)	JEV negative, no. (%)	Prevalence odds ratio	95% CI	P-value
Occupation					
Abattoir or meat worker	0 (0.0)	7 (0.9)	0.00	0.00–16.34	1.000
Animal shooter or hunter	1 (3.7)	19 (2.4)	1.55	0.04–10.55	0.495

Council worker (Environmental Health Officer or outdoor staff)	0 (0.0)	11 (1.4)	0.00	0.00–10.28	1.000
Animal transport driver	1 (3.7)	8 (1.0)	3.74	0.08–29.62	0.263
Pig farmer or worker	0 (0.0)	6 (0.8)	0.00	0.00–19.12	1.000
Pest controller	1 (3.7)	7 (0.9)	4.28	0.09–35.24	0.238
Other type of farmer	7 (25.9)	124 (15.8)	1.87	0.65–4.72	0.179
Laboratory worker	0 (0.0)	8 (1.0)	0.00	0.00–14.25	1.000
Veterinarian	1 (3.7)	1 (0.1)	30.19	0.37–2372.37	0.065
Vet technician or nurse	0 (0.0)	3 (0.4)	0.00	0.00–38.50	1.000
Wildlife or zoo worker	0 (0.0)	3 (0.4)	0.00	0.00–38.50	1.000
Other outdoor occupation	1 (3.7)	47 (6.0)	0.60	0.01–3.86	1.000
Activities and locations†					
Piggery‡	2 (7.4)	29 (3.7)	2.03	0.22–8.87	0.285
Abattoir	1 (3.7)	15 (1.9)	1.98	0.05–13.83	0.420
Agricultural show	4 (14.8)	69 (8.8)	1.81	0.44–5.50	0.293
Farm	14 (51.9)	368 (46.8)	1.22	0.53–2.87	0.696
States or National Parks	10 (37.0)	368 (46.8)	0.67	0.27–1.57	0.335
Camping	7 (25.9)	285 (36.3)	0.62	0.22–1.54	0.313
Fishing (fresh water)	6 (22.2)	199 (25.3)	0.84	0.27–2.20	0.825
Hunting	2 (7.4)	36 (4.6)	1.67	0.18–7.13	0.363
Bush walking or hiking	12 (44.4)	353 (44.9)	0.98	0.41–2.28	1.000
Water sports or boating	4 (14.8)	182 (23.2)	0.58	0.14–1.72	0.483
Gardening or horticulture	20 (74.1)	611 (77.7)	0.82	0.33–2.33	0.641
Picnicking	7 (25.9)	254 (32.3)	0.73	0.26–1.83	0.538
Outdoor sports	6 (22.2)	259 (33.0)	0.58	0.19–1.51	0.300
Animal exposure§					
Mosquitoes	20 (74.1)	669 (85.1)	0.50	0.20–1.43	0.166
Birds	13 (48.2)	408 (51.9)	0.86	0.37–2.00	0.845
Domestic pigs	0 (0.0)	10 (1.3)	0.00	0.00–11.34	1.000
Feral pigs	2 (7.4)	3 (0.4)	20.88	1.65–188.07	0.010
Horses	2 (7.4)	113 (14.4)	0.48	0.05–1.96	0.409
Bats	0 (0.0)	41 (5.2)	0.00	0.00–2.61	0.392
Protective factors					
Mosquito repellent when outdoors	21 (77.8)	613 (78.0)	0.99	0.38–3.04	1.000
Mosquito repellent when mosquitoes about	22 (81.5)	693 (88.2)	0.59	0.21–2.05	0.359
Wearing protective clothes outside in summer	25 (92.6)	623 (79.3)	3.27	0.80–28.74	0.140
Using mosquito preventing devices	15 (55.6)	533 (67.8)	0.59	0.26–1.41	0.211
Presence of insect screens at home	26 (96.3)	776 (98.7)	0.34	0.04–15.09	0.312

† Visited location or participated in activity since 1 December 2021.

‡ Lived or worked in close proximity (within 5km) since 1 December 2021, participants who answered “unsure” (n=50) were excluded from POR calculations.

§ Had exposure or close contact since 1 December 2021.

Time spent outdoors was compared for occupation, recreation and total time (Table 5). More seropositive participants (33.3%) reported spending all of their time outdoors at dawn or dusk compared with seronegative participants (23.2%). However, no statistically significant difference in the total time spent outdoors ($p=0.843$) or time spent outdoors at dawn or dusk ($p=0.815$) was found.

Table 5: Hours per day reported to be spent outdoors

Hours spent outdoors	Occupational time spent outdoors		Recreational time spent outdoors		Total time spent outdoors	
	JEV positive (n) (%)	JEV negative (n) (%)	JEV positive (n) (%)	JEV negative (n) (%)	JEV positive (n) (%)	JEV negative (n) (%)
<2 hours	12 (44.4)	293 (37.3)	8 (29.6)	265 (33.7)	7 (25.9)	192 (24.4)
2 – 4 hours	7 (25.9)	283 (36.0)	10 (37.0)	334 (42.5)	5 (18.5)	135 (17.2)
4 – 8 hours	5 (18.5)	162 (20.6)	6 (22.2)	157 (20.0)	7 (25.9)	231 (29.4)
>8 hours	3 (11.1)	48 (6.1)	3 (11.1)	30 (3.8)	8 (29.6)	228 (29.0)

None of the investigated activities and locations were significantly associated with JEV infection ($p>0.05$) (Table 4). The only behavioural factor identified to be significantly associated with infection was exposure to feral pigs (POR 20.88, 95% CI 1.65-188.07, $p=0.01$). However, the number of participants reporting this risk factor was small (n=5), and all reported infrequent contact (a few times a year).

Although not statistically significant (Table 4), seropositive participants reported more frequent exposure to some investigated factors. For example, 37.0% of seropositive participants reported daily exposure to mosquitoes compared with 24.2% of seronegative participants, 40.7% of seropositive participants reported visiting farms at least a few times a month compared with 29.0% of seronegative participants, and 11.1% of seropositive participants reported fishing at least a few times a month compared to 4.8% of seronegative participants.

Compared with participants who tested seronegative, seropositive participants were less likely to use mosquito devices (POR=0.59), insect screens (POR=0.34) or mosquito repellent when noticing mosquitoes were present (POR=0.59). None of these results were statistically significant ($p>0.05$) (Table 4).

Sub-analysis (household members)

Eighteen household members, who resided with seropositive participants (principal cases), were invited to participate in the study if they had not already participated. Nine (50.0%) chose to participate, of whom four had previously been recruited into the study through opportunistic or targeted methods, and five were household recruits. Of the participating household members, two (22.2%) were seropositive, both were partners of a seropositive participant who had been recruited through opportunistic (n=1) or targeted (n=1) methods. No additional seropositive persons were detected through household recruitment. In one of the households containing a pair of seropositive participants, an additional household recruit was seronegative.

DISCUSSION

These results suggest that during the 2022 outbreak in northern Victoria, many more people than initially reported may have been exposed to JEV, and that there continues to be widespread population vulnerability to infection. This demonstrates that an evidence-based ongoing vaccination program alongside other prevention strategies is required to reduce the risk of human infection and clinical disease during future mosquito seasons.

Whilst the literature indicates children are at greatest risk of JEV infection in endemic countries [1, 3, 17], these results suggest that in this immunologically naïve population, risk increased with increasing age, with older adults at greatest risk. A similar trend was reported in a serosurvey conducted in NSW following the 2022 outbreak [31]. Further research is needed to understand why older age appears to be more of a risk factor for JEV infection in populations naïve to the virus. Potential hypotheses include age-related changes to immunity, differing exposures associated with age (e.g. occupational status), or the lifetime risk of exposure from prior travel. It is also possible that older seropositive participants may have been exposed to Murray Valley encephalitis virus during the 1974 outbreak in Victoria (92.6% of seropositive participants were aged ≥ 50 years) and that our results have been influenced by cross-reactivity [32]. We also cannot exclude that JEV may have circulated undetected in south-eastern Australia in the past, however no other evidence supports this. Whilst the cause of this association is unclear, these results support early policy decision-making which restricted vaccines to adults ≥ 50 years in the context of limited vaccine supply.

Although sex was not found to be a statistically significant risk factor in this study, it was notable that whilst the sample was skewed towards being female (61.0%), approximately half of seropositive participants were male. Prior research in endemic regions has suggested

males are more likely than females to become infected with JEV, experience clinical illness and have poor outcomes, with this pattern observed across all age groups [5, 8, 16, 17, 33]. Given that this was also observed in the initial outbreak in Victoria in 2022, where over half (7 of 13) reported JE cases were in older males ≥ 60 years [34], further investigation into the differences in sex distribution in immunologically naïve populations is warranted.

Aside from older age, the only other factor found to be significantly associated with JEV infection was contact with feral pigs. Whilst the overall sample reporting this exposure was small and the contact infrequent, further investigation is required to determine the strength of this association given that pigs are the central amplifying host for JEV. Animal surveillance of JEV in Victoria has focussed on domestic piggeries. Our results suggest that contact with wild pigs may also pose a threat, with JEV being detected in feral pigs in other Australian states and territories during the 2022 outbreak [35]. It would be beneficial to expand current animal surveillance programs to include wild pig populations to better define this risk, particularly if any future efforts were made to reduce the reservoir through removal of piggeries from population centres or animal culling, as implemented in some Asian countries [36].

The seropositivity we observed among household members (22.2%) was high compared to the general population (3.3%) (primary analysis). However, as the total sample included in the household sub-analysis was very small, and not all household members chose to participate, this has likely introduced selection bias. There is merit to further exploring the association between residing in the same household and JEV infection, given the implications for a vaccination program, which could prioritise household members of JE cases in the future as part of public health follow-up.

This study was conducted as part of a broader body of national serosurveillance work following the 2022 outbreak in south-eastern Australia. Results from the NSW serosurvey showed 8.7% of participants had evidence of prior JEV infection [31], a higher seropositivity rate than observed in this study. This may reflect a true difference, with the risk of infection influenced by geographical exposures. However, this difference could also be due to differences in testing methodologies, or differing recruitment strategies, with the NSW serosurvey solely utilising targeted methods such as advertising and community outreach. The results of our study showed a slightly lower seropositivity rate among participants recruited opportunistically compared to targeted strategies, suggesting self-selection bias may be influencing these results. Further results from serosurveys underway in other states and territories may shed further light on these discrepancies, and provide additional evidence to support policy approaches to JEV in the region.

There were several limitations in this study. The overall sample was skewed towards older age and female sex. Most participants were recruited opportunistically, and whilst this was intended to be a representative sample, participants may have been presenting for blood tests due to underlying medical conditions, leading to the seropositivity being either over- or underestimated. The sample of household members was too small to provide adequate sampling power and some household members were recruited through opportunistic or targeted methods, which meant they were included in both the primary and sub-analysis. The sample of some categories of reported occupations, activities and hobbies, and for certain population groups, such as Aboriginal and Torres Strait Islanders, was also too small to provide adequate sampling power to investigate potential associations. Consolidation of results across the national serosurveillance program will provide additional sampling power to support further investigation of these factors. The questionnaire was based on available literature and local epidemiological evidence from JE cases [37], however was not validated. Most questions asked participants to consider exposures over the past six months, and there may have been recall bias or acquiescence bias, for example with participants overestimating their use of protective factors. The study was conducted across a region in northern Victoria, and recruitment varied by geography. Recruitment was hampered in some areas due to extensive flooding occurring in northern Victoria throughout October and November 2022. These factors may have influenced the estimated seropositivity of this study. Interpretation of serology results can pose challenges and, though unlikely, some participants may have been misclassified as seronegative or seropositive, and laboratory results may have also been influenced by cross-reactivity. The ERP was intended to minimise errors in the classification of results, however some participants were unable to complete requested re-bleeds due to being vaccinated in the period after their initial test or being loss to follow-up. The ERP classified these participants as seronegative as the initial results were considered likely false positives.

Despite these limitations, this study supports a greater understanding of JEV infection in northern Victoria following the outbreak, and risk factors for JEV infection in immunologically naïve populations. The results suggest that population vulnerability to JEV remains widespread and there are few consistent risk factors for infection. This demonstrates the challenges of implementing an evidence-based vaccine strategy in the context of limited supply, and highlights the need for ongoing research to determine optimal vaccine strategies in the future. Whilst it was initially unknown whether JEV would emerge in future mosquito seasons, the re-emergence of cases in south-eastern Australia in December 2022 indicates the virus may become endemic to the region [38-40]. Within this context, it may be necessary to implement a population wide vaccination strategy to prevent future infections in Victoria.

This research has implications for other immunologically naïve populations across Australia and internationally, with the potential for JEV to emerge in new susceptible regions in the future [7, 41].

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APPENDIX A: ROLES AND RESPONSIBILITIES OF CO-LEAD INVESTIGATORS

The Japanese encephalitis (JE) serosurvey conducted in northern Victoria was jointly led by two MAE scholars, Maddy Marsland and Tilda Thomson. This document has been prepared for the purposes of clarifying roles and responsibilities within the MAE thesis to demonstrate core competencies.

Components are listed as being led by 'Maddy', 'Tilda', or 'Both'. Where the component is listed as being led by an individual, this scholar undertook the majority of related work, with the other scholar providing critical review, input and feedback. Where the component is listed as being led by both scholars, equal contribution was made. Many other investigators provided critical review and contribution to many aspects of this work, however for the purposes of the MAE thesis only the roles of the two co-lead investigators are listed.

COMPONENT	LEAD
STUDY DESIGN	
Literature review (see Appendix B)	Both
Developed study protocol in collaboration with other investigators	Both
Conducted sample size calculations	Tilda
Developed questionnaire for study participants	Maddy
Developed follow-up questionnaire for participants who tested positive	Tilda
Designed questionnaires in Microsoft Forms	Both
Developed participant information sheet	Tilda
Developed child participant information sheet	Tilda
Coordinated development of study pathology form	Both
Developed procedures for managing results and informing participants of results	Both
Developed information sheet and notification for negative participants (see Appendix C)	Maddy
Developed information sheet and notification for positive participants (see Appendix C)	Maddy
Developed procedures for managing laboratory results, matching to questionnaire data, perform preliminary data cleaning, and record method and date of communication of results to participants	Tilda
Developed PowerBI report to monitor and clean laboratory results data	Tilda
Coordinated obtaining ethics approval and submission of amendments	Both
Coordinated budget documentation and planning	Both
Storage of study documentation, hard copy laboratory results and relevant correspondence in the Department's official record keeping system	Tilda
STUDY COORDINATION	
Pre-briefed local public health units on recruitment	Both
Developed Frequently Asked Questions for Public Health Officers	Both
Coordinated laboratory components of the study	Both
Coordinated with pathology collectors (meetings and documentation)	Both
Coordinated expansion to additional locations (including additional pathology sites)	Both
Coordinated documentation for and sat on Expert Review Panel for test results	Both
Coordinated and monitored incoming laboratory results	Both
Provided central coordination and liaised with Local Public Health Units	Both
Coordinated and chaired regular meetings	Both

Coordinated notification of participants requiring follow-up by Local Public Health Units (for missing questionnaire data)	Maddy
Contacted participants to seek missing questionnaire information (where not able to be completed by Local Public Health Units)	Tilda
Coordinated notification of participants requiring follow-up (positive results)	Both
Contacted positive participants to notify results, complete follow-up questionnaire and recruit household members (where not able to be completed by Local Public Health Units)	Maddy
Responded to questions from public health officers and participants	Both
STAKEHOLDER ENGAGEMENT	
Provided regular updates to all stakeholders on recruitment and preliminary results	Both
Liaised with and managed relationships with key study partners and stakeholders	Both
Provided study materials to other jurisdictions to support future studies	Both
Represented study team at a range of official meetings, including in support of broader JEV preparedness activities	Both
DATA ANALYSIS	
Developed data analysis plan	Both
Undertook cleaning of data	Both
Cleaning of risk factor data (age, occupation)	Maddy
Cleaning of location and environmental data (addresses)	Tilda
Undertook analysis of data	Both
Descriptive analysis – demographics, risk factors and protective factors	Maddy
Descriptive analysis – location and environmental factors	Tilda
Descriptive analysis – household sub-analysis	Maddy
Mapping of results by location (creating figures for presentations and publication, including map of recruitment locations)	Tilda
Calculation of prevalence odds ratios for demographic and behavioural factors	Maddy
Calculation of prevalence odds ratios for environmental risk factors	Tilda
MEDIA AND COMMUNICATIONS	
Developed advertising materials, posters and community notices	Both
Developed web content and provided input to CHO media alert to support study recruitment	Maddy
Provided responses to media enquiries during study recruitment	Maddy
Assisted with media releases related to literature review and serosurvey results	Both
PRESENTATIONS AND DISSEMINATION OF RESULTS	
Developed 2-page summary of provisional results for public release and participants (see Appendix D)	Maddy
Developed slides for DCHO and CHO presentations on provisional results	Both
Prepared and presented at a range of internal and external meetings	Both
Coordinated and led write-up of peer-reviewed publication of results (see Appendix F)	Both

APPENDIX B: LITERATURE REVIEW

Japanese encephalitis: A rapid review of reported prevalence of infection, clinical disease and sequelae in immunologically naive populations to inform Australia's response

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Key words: emerging infectious disease, epidemiology, vector-borne disease

Japanese encephalitis virus (JEV) is a zoonotic flavivirus primarily transmitted via *Culex* mosquitoes.^{1,2} Most infections are asymptomatic, however, a minority result in Japanese encephalitis (JE), which causes significant morbidity and mortality. The case fatality rate is reported to be between 20%–30%^{1,3} and 30%–50% of cases experience neurological sequelae.^{1,3,4}

Australia is largely immunologically naive to JEV. Prior to 2022, the southerly limit of reported disease was the far North.⁵ However, locally acquired cases of JE were reported in South-Eastern Australia in March 2022. The emergence of the virus poses a significant threat to human health.

For public health decision-making in response to this outbreak, it is important to understand within immunologically naive populations.

- What proportion of JEV infections develop clinical disease?
- What proportion of JE cases result in long-term sequelae and/or death?
- What are the key risk factors for JEV infection and developing JE?

We conducted a rapid and focussed review of available evidence from similar populations and synthesised findings to inform public health planning, including all available evidence prior to May 2022, when this review was conducted.

A search strategy was devised and refined to specify populations of interest, given many studies initially identified were from JEV endemic regions. The search terms used were (“Japanese encephalitis”) AND (“non endemic” OR “naive” OR “non immune” OR “at risk” OR “military” OR “immigrant” OR “travel*” OR “tourist” OR “serosurvey”). More specific search terms (e.g. “risk factor”) excessively narrowed the search, and for the purposes of this review, it was pertinent to include broader studies with relevant findings.

The search engines used were PubMed, Scopus, Embase and Google Scholar. Searches were restricted to English language. Single case reports, newspaper articles and papers concerning animal populations or JEV endemic populations were excluded. Two researchers screened titles and abstracts for relevance. All papers identified were then reviewed in full by both researchers. Reference lists were examined to identify further relevant literature.

Summary of available evidence

Three categories of immunologically naive populations were identified: military personnel deployed in Asia; travellers to Asia from non-endemic areas; and residents in areas where JE was newly detected. Generally, studies did not consistently distinguish between non-encephalitic and encephalitic clinical disease associated with JEV infection, so all individuals with severe disease are referred to as JE cases.

Prevalence of infection

Estimates of seroprevalence varied (see Table 1), and interpretation of these results is restricted by methodological differences between the studies and differing exposure levels to JEV. In military units, seroprevalences ranged from 0%–4.5% in prospective studies to 5.3%–27% in retrospective studies where cases of JE had been identified.^{6–8} Studies in areas where JE had been newly detected also reported varied seroprevalences, ranging from 2.4% in Hong Kong,⁹ 4.3% in Saipan, Northern Mariana Islands,¹⁰ 9.4% in Papua, Indonesia,¹¹ 9.9% in Tibet, China¹² and 16% on Badu Island, Torres Strait, Australia.¹³ JEV infection was generally not reported in travellers, however, one prospective study of 387 Australian travellers to Asia reported no infections.¹⁴ While the variability of these results is

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Table 1: Key sources describing Japanese encephalitis in military, travellers, and residents in areas where JE was newly detected.

Study	Population	Study type	Seroprevalence	Incidence of JE cases	Comparison of clinical to subclinical cases	Sequelae among JE cases	Case fatality rate among JE cases	Comments
Military								
Benenson et al., 1975 ⁸	United States military in Thailand	Case series and serosurvey	27% (n=88)	4.3 per 1,000	Estimated 1:63 clinical to subclinical ratio	N/A	0% (n=0)	2,101 personnel in 5 units, 9 cases of JE, 329 included in serosurvey.
Chu et al., 1960 ²⁸	United States military in Taiwan	Serosurvey	4.5% (n=7)	0% (n=0)	N/A	N/A	N/A	154 included in serosurvey.
	United States military in Okinawa, Japan		3.8% (n=8)	0% (n=0)	N/A	N/A	N/A	211 included in serosurvey.
Eick-cost et al., 2015 ²⁹	United States military in Korea	Serosurvey	0.2% (n=2)	0% (n=0)	N/A	N/A	N/A	1,000 included in serosurvey, no cases of JE.
Halstead et al., 1962 ⁶	United States military in Korea	Case series and serosurvey	9.3% (n=28)	3.7 per 1,000 (3 cases in ~800 personnel in Kunsan)	1:25 clinical to subclinical ratio	N/A	0% (n=0)	400 included in serosurvey at Kunsan, 3 cases of JE.
			5.3% (n=7)		1:48 clinical to subclinical ratio	N/A	0% (n=0)	131 included in serosurvey in Osan, 4 cases of JE.
			3.4% (n=6)		>170:1 clinical to subclinical ratio	N/A	N/A	178 included in serosurvey in Pusan, no cases of JE.
Hsieh et al., 1963 ⁷	United States military in Okinawa, Japan	Serosurvey	19.2% (n=50)	0.92 per 1,000	1:200 estimated clinical to subclinical ratio	N/A	N/A	1,083 personnel in battalion, 1 case of JE, 260 included in serosurvey.
Lincoln et al., 1952 ²³	United States military in Pusan, Korea	Case series	N/A	N/A	N/A	N/A	8.5% (n=17)	201 cases of JE.
Travellers								
Buhl et al., 2009 ¹⁶	Travellers from non-endemic countries to Asia	Review of published or reported cases	N/A	0.0025 per 1,000 travellers regardless of type/length of stay	N/A	43% (n=9)	19% (n=4)	21 cases in travellers published or anecdotally reported between 1992 to 2008.
Erra et al., 2015 ²⁰	Travellers from non-endemic countries to endemic countries	Review of published case reports	N/A	N/A	N/A	51% (n=29)	23% (n=13)	67 cases among travellers to Asia.
Hills et al., 2010 ⁴	Travellers from non-endemic countries to endemic countries	Review of published case reports	N/A	<0.0002 per 1,000 travellers (states unlikely >1 case per 1 million travellers)	N/A	44% (n=24)	18% (n=10)	55 cases from citizens of 17 non-endemic countries. Study estimates that at least 50% of cases are published in literature.
Hills et al., 2019 ³	Travellers from non-endemic countries to endemic countries	Review of published or reported cases	N/A	N/A	N/A	46% (n=39)	16% (n=14)	Reported 85 cases from 1973–2017. 15% (n=13) had unknown outcomes.
	United States travellers to endemic regions		N/A	<0.001 per 1,000 trips to endemic regions	N/A	25% (n=3)	17% (n=2)	Reported 12 cases from 1993–2017. 8% (n=1) had unknown outcomes.
Pavli et al., 2015 ²²	Travellers from non-endemic countries to endemic countries	Review of published case reports	N/A	N/A	N/A	28.2% (n=11)	15.4% (n=6)	39 travel-related cases from 1992–2014.
Tsai, 1993 ¹⁵	United States travellers to endemic countries	Review of reported cases	N/A	0.05 – 0.2 per 1,000 travellers per week	N/A	N/A	N/A	Estimate for risk based on an estimated annual incidence rate of 10 per 10,000 in the endemic region.
Residents in areas where JE was newly detected								
McNaughton et al., 2018 ²¹	Residents of Sonitpur District, Assam, India	Case series	N/A	N/A	N/A	47% (n=21)	24% (n=11)	45 cases in a previously unaffected region, however endemicity uncertain.
Partridge et al., 2007 ¹⁷	Residents of Kathmandu Valley, Nepal	Case series	N/A	0.021 per 1,000	N/A	N/A	20% (n=8)	40 cases in a previously unaffected region, however endemicity uncertain.

N/A = not applicable.

difficult to apply to the Australian context, the studies of military personnel in particular demonstrate that significant transmission can occur within short timeframes in immunologically naive populations.

Clinical disease

Only studies in military populations have considered the ratio of clinical to subclinical disease in immunologically naive populations, with estimates ranging from 1:25 to 1:200 (see Table 1).^{6–8} These studies report the number of JE cases, the seroprevalence and the size of the population (to estimate the total number of JEV infections). Many other studies report some of these elements but without sufficient information to estimate a clinical to subclinical ratio.

While very high attack rates of JEV infection and JE have been reported among military populations, these represent small study populations of ~1,000 to ~2,000 personnel (see Table 1) who may not be comparable to the general Australian population.^{6–8} However, the high incidence of JE among generally young and healthy populations is cause for concern.

Estimates of the risk of JE among travellers ranged from <0.0002 to 0.2 per 1,000 travellers (Table 1).^{3,4,15,16} However, this may also not be applicable to the Australian population in the context of ongoing local exposure.

Within regions where JE was newly detected, the estimated incidence ranged from 1.5 to 2.1 per 100,000 cases in Kathmandu Valley, Nepal to 25 per 100,000 cases in Saipan, Northern Mariana Islands.^{10,17,18} Importantly, most studies did not specify the clinical case definitions used, referring to JE cases as those with severe systemic and/or neurological illness.

Clinical outcomes

Rates of sequelae and fatality appear similar across endemic and non-endemic populations.¹⁹ Clinical sequelae associated with JE were not well defined, and most studies did not include a specific definition.^{3,16,20} The reported proportion of long-term neurological, cognitive, or behavioural sequelae among JE cases in immunologically naive populations ranged from 25% to 51% (see Table 1).^{3,4,16,20–22} This is consistent with the 30%–50% reported in endemic populations.^{1,3,4} Most studies reporting long-term sequelae focussed on travel-associated JE.^{3,4,16,20,22} Long-term outcomes of these cases were often unknown, which may have led to the rate of long-term sequelae being underestimated. One study in a region where JE was newly detected found that 47% of cases experienced long-term sequelae.²¹

The case fatality rate (CFR) reported among JE cases from immunologically naive populations ranged from 0% to 24% (see Table 1).^{3,4,6,8,16,17,20–23} This slightly differs from the 20%–30% CFR reported in endemic populations.^{1,3} This difference may be attributed to population demographics, with low CFRs reported in the studies of military personnel,^{6,8} or differences in surveillance practices resulting in lower case ascertainment. CFRs were higher among studies investigating travel-associated JE cases and in regions where JE was newly reported, and these studies may better reflect the Australian context.^{3,4,16,17,20,21}

Risk factors

Understanding risk factors for JEV infection, developing JE and experiencing poor outcomes are essential for implementing effective

prevention strategies. However, few studies investigate risk factors, and it remains unclear why some locations with similar seroprevalence experienced different disease severity.^{6,15}

In endemic countries, JEV infection and JE are primarily seen in children, as most adults achieve immunity during childhood.¹ However, the age distribution differs in immunologically naive populations, with a median age ~30–35 years for JE cases.^{3,4,10,20,21} Some studies have shown a J-shaped age-specific incidence for JE,²⁴ while others have shown the incidence decreasing with age.¹² Some studies suggest age is a risk factor for death among JE cases.^{4,16}

Other than age, factors related to mosquito exposure are most commonly associated with JEV infection and JE cases. Several studies noted a higher seroprevalence and incidence of disease in residents and travellers to rural areas compared to urban areas.^{4,12,14,25} In Southeast Asia, the risk of infection may be higher during the rainy season when mosquito breeding is common.¹⁶ However, it was emphasised that JE has occurred in travellers with minimal rural travel and outside of the usual seasonal patterns.^{16,22}

Few studies investigated risk factors for poor outcomes among JE cases from immunologically naive populations. Several studies noted a greater incidence of JE and deaths among males compared to females.^{3,17,20} However, these had small study populations and may reflect the specific demographics of these populations.

Limitations

Studies in military personnel were restricted to groups of young and healthy males who may reflect a lower risk group compared to the general population. Studies focussed on JE in travellers noted that approximately half of travel-associated JE cases are published.^{4,16,22} Furthermore, many of the studies in regions where JE was newly detected were located within endemic countries; therefore, the true immunological status of these populations is uncertain. Variation in case definitions and surveillance methods may account for the differences observed, which hinder our ability to generalise findings to the Australian population. Results must therefore be interpreted with caution.

Implications for Australia

There is limited research on JEV and JE in immunologically naive populations. Based on the research available, it is uncertain what proportion of immunologically naive people in Australia are at risk of JE. However, the proportion of JE cases who develop sequelae and/or die remains very high.

Other than the presence of a reservoir and vector distribution, risk factors for JEV infection and progressing to JE and death are not well understood. Australia has progressively expanded vaccine eligibility throughout 2022 based on our emerging understanding of groups at higher risk. However, the evidence from human studies to support this decision-making has been very limited and of variable quality.

Ongoing serosurveillance at a state and national level will support a better understanding of JEV in the local context, including the distribution of and risk factors for infection. Results from New South Wales suggest 8.7% of serosurvey participants had evidence of prior JEV infection,²⁶ indicating that many people may have been infected during the outbreak, but also that there is widespread population vulnerability to infection. Results from additional serosurveys will inform further vaccine prioritisation.

In the setting of finite vaccine supply, mass vaccination has not been feasible ahead of the current mosquito season. Alternative and additional public health actions are required to mitigate the potential for significant outbreaks of JEV. Apart from sporadic cases and small outbreaks of Murray Valley encephalitis,²⁷ South-Eastern Australia has not experienced a mosquito-borne illness with the severity of JE, so there are varying levels of awareness regarding the need for mosquito bite protection. Consequently, a strong targeted public education and prevention campaign is essential to reduce the risk to travellers and residents in high-risk areas.

Further research, including serosurveillance, is needed to understand the possible impacts of JEV within the Australian context. Cases of JE have been reported in South-Eastern Australia in January 2023. While the future is uncertain, this suggests that JEV may become endemic to Australia. The public health implications of this cannot be understated. While a minority of individuals who are infected with JEV will develop JE, for these individuals, the consequences can be devastating. At a population level, if JEV were to move unmitigated through the Australian community, the associated morbidity and mortality could be significant.

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Ethical information

Ethical approval was not required for this review.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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APPENDIX C: INFORMATION SHEETS

Participants who test negative to Japanese Encephalitis Virus

I have tested negative for Japanese Encephalitis Virus (JEV), what does this mean?

We tested your blood for antibodies to JEV. Your body makes antibodies when it fights an infection or when you are vaccinated against an infection. Your test results show that you do not have any antibodies for JEV. This means you have not been infected with JEV in the past and may be at risk of being infected with JEV in the future. We cannot be certain whether JEV will occur in the Victorian community again during future mosquito seasons.

How is JEV transmitted?

JEV is spread to humans through the bite of an infected mosquito. The virus can also infect birds and pigs. However, the virus cannot be spread directly from person to person or to people from other animals.

How can I protect myself?

You can protect yourself from JEV by avoiding mosquito bites.

Steps to protect yourself and your family against mosquito-borne diseases include:

- Wearing long, loose fitting clothes outdoors.
- Using mosquito repellents containing picaridin or DEET on all exposed skin.
- Limiting outdoor activity if lots of mosquitoes are about.
- Using 'knockdown' fly sprays and plug-in repellent devices indoors.
- Using mosquito coils in small outdoor areas where you gather to sit or eat.
- Making sure your accommodation is mosquito-proof.
- Sleeping under mosquito nets treated with insecticides if you don't have flywire screens on windows on your home or are sleeping in an untreated tent or out in the open.
- Making sure there is no stagnant water around your home.

Will I be able to be vaccinated for JEV?

There is a vaccine available to protect against JEV. However, currently there is a limited amount of vaccine available within Australia. Vaccines are being prioritised to groups in the community who are at higher risk of infection and experiencing severe disease. This initially included people who live or work at piggeries or who work in mosquito control.

[Vaccine recommendations are being regularly reviewed](#) as more vaccine becomes available and we learn more about the virus (similar to the COVID-19 vaccine rollout). Serosurveys being conducted around the country, including this one, will provide important information to help inform these vaccine recommendations. As with any vaccine, you should discuss the risks and benefits with your doctor. Your doctor will also be able to guide you about whether you are recommended to be vaccinated.

Where can I find more information?

There is information about JEV (including prevention) available online:

Victorian Department of Health:

<https://www.health.vic.gov.au/infectious-diseases/information-for-the-public-japanese-encephalitis-in-victoria>

Better Health:

<https://www.betterhealth.vic.gov.au/japanese-encephalitis>

<https://www.betterhealth.vic.gov.au/campaigns/beat-bite>

Participants who test positive to Japanese Encephalitis Virus

I have tested positive for Japanese Encephalitis Virus (JEV), what does this mean?

We tested your blood for antibodies to JEV. Your body makes antibodies when it fights an infection or when you are vaccinated against an infection. Your test results show that you have antibodies for JEV. This means you have been infected with JEV in the past. Many people with JEV have no symptoms, so it is likely you were not aware when you were infected with JEV.

As you would have discussed with your Local Public Health Unit, there is no risk associated with having previously had JEV infection and there will be no long-term impacts. Prior infection with JEV is also thought to provide lifelong immunity, so it is unlikely that you will develop JEV again in the future. However, you should still take precautions to protect yourself and other household members against JEV.

How is JEV transmitted?

JEV is spread to humans through the bite of an infected mosquito. The virus can also infect birds and pigs. However, the virus cannot be spread directly from person to person or to people from other animals.

How can I protect myself?

You can protect yourself from JEV by avoiding mosquito bites.

Steps to protect yourself and your family against mosquito-borne diseases include:

- Wearing long, loose fitting clothes outdoors.
- Using mosquito repellents containing picaridin or DEET on all exposed skin.
- Limiting outdoor activity if lots of mosquitoes are about.
- Using 'knockdown' fly sprays and plug-in repellent devices indoors.
- Using mosquito coils in small outdoor areas where you gather to sit or eat.
- Making sure your accommodation is mosquito-proof.
- Sleeping under mosquito nets treated with insecticides if you don't have flywire screens on windows on your home or are sleeping in an untreated tent or out in the open.
- Making sure there is no stagnant water around your home.

Do I need to be vaccinated for JEV?

Prior infection with JEV typically provides lifelong immunity. If you have tested positive, you do not need to be vaccinated for JEV. However, if you have any concerns about whether you should be vaccinated, you can discuss this with your doctor. Your doctor will also be able to guide you about whether you are recommended to be vaccinated.

Can someone else be vaccinated for JEV (e.g. a family member)?

There is a vaccine available to protect against JEV. However, currently there is a limited amount of vaccine available within Australia. Vaccines are being prioritised to groups in the community who are at higher risk of infection and experiencing severe disease. This initially included people who live or work at piggeries or who work in mosquito control.

[Vaccine recommendations are being regularly reviewed](#) as more vaccine becomes available and we learn more about the virus (similar to the COVID-19 vaccine rollout). Serosurveys being conducted around the country, including this one, will provide important information to help inform these vaccine recommendations. As with any vaccine, you should discuss the risks and benefits with your doctor. Your doctor will also be able to guide you about whether you are recommended to be vaccinated.

Where can I find more information?

There is information about JEV (including prevention) available online:

Victorian Department of Health:

<https://www.health.vic.gov.au/infectious-diseases/information-for-the-public-japanese-encephalitis-in-victoria>

Better Health:

<https://www.betterhealth.vic.gov.au/japanese-encephalitis>

<https://www.betterhealth.vic.gov.au/campaigns/beat-bite>

APPENDIX D: LAY SUMMARY

Japanese encephalitis virus (JEV) serosurvey in northern Victoria

Summary of results

What is Japanese encephalitis virus?

Japanese encephalitis virus (JEV) is an infection that is spread to humans through the bite of an infected mosquito. Most people who get infected with JEV have mild symptoms or no symptoms at all. However, JEV can cause Japanese encephalitis (JE), a rare but potentially serious infection of the brain.

What was this study about?

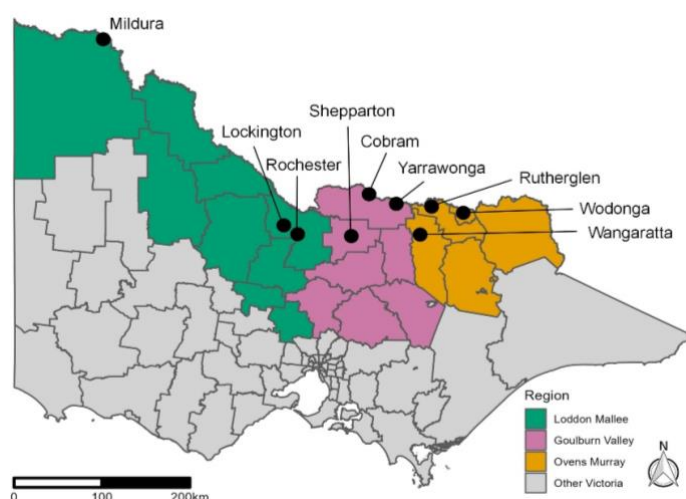
In early 2022, JEV was detected in humans, pigs, and mosquitoes in Victoria for the first time. This study aimed to help us understand how widespread JEV infection is in northern Victoria and which people are most likely to become infected. This information informs our public health planning and prevention strategies.

How was this study conducted?

People were asked to join the study either when they were having a routine blood test at a pathology collection centre (see Figure 1), through community outreach, or after a household member tested positive in the serosurvey. People were excluded if they had previously been diagnosed with or were already vaccinated for JE or were born in a JEV endemic country.

All participants completed a questionnaire and had their blood tested for evidence of prior JEV infection. Blood testing was performed at a reference laboratory in Victoria and sent to another laboratory in New South Wales for confirmation.

Figure 1: Primary recruitment locations



What did the study find?

Who participated?

A total of 820 people completed a questionnaire and provided a blood sample for this study. Of these, 561 (68%) were recruited in the Ovens Murray region, 195 (24%) were recruited in the Goulburn Valley region, and 64 (8%) were recruited in the Loddon Mallee region. Participants were aged between 7 and 92, with a median age of 59 years. The majority of participants (61%) were female.

Results

In total, 27 out of 820 (3.3%) participants were found to have evidence of prior JEV infection, equal to about one in thirty.

- Participants who tested positive were aged between 25 and 90 with a median average age of 73.
- A majority of those who tested positive were male (14/27, 52%).
- Participants who had evidence of prior JEV infection were found in all three regions (Figure 1).

Limitations

- These results are an estimate only. Participation in this study was voluntary and this may have influenced those who participated in the study. The proportion of people who tested positive was different in different areas (higher or lower than the overall estimate). In some areas, only a small number of participants were recruited which may have influenced the overall estimate.
- The results may be biased (too low or too high) if the participants recruited to the study were not representative of the population living, working, or visiting these areas. For example, our sample was a predominantly female and older population, which may have influenced the results.

Next steps

These results are preliminary. The results of the full analysis will be made publicly available at a later date.

These results suggest that people living in or visiting northern Victoria may be at risk of JEV infection and should take steps to limit their exposure to mosquitoes during peak mosquito season in the warmer months, from October to March. Mosquitoes can also transmit other viruses such as Ross River virus, Barmah Forest virus, Murray Valley encephalitis virus or Kunjin virus. A vaccine is available to protect against JEV infection.

For more information on how to protect yourself and others against mosquito-borne diseases, visit:

<https://www.betterhealth.vic.gov.au/protect-yourself-mosquito-borne-disease>

Who was involved in this study?

The Department of Health would like to thank all participants who volunteered to be part of this study. We also acknowledge and thank all investigators and collaborators involved with this study:

- Ovens Murray and Goulburn Valley Public Health Units
- Victorian Infectious Diseases Reference Laboratory and Institute of Clinical and Medical Pathology in New South Wales
- Dorevitch Pathology and Austin Pathology
- Monash University Rural Health Mildura
- The National Centre for Immunisation Research and Surveillance

Where can I get more information?

More information about Japanese encephalitis is available online at:

<https://www.health.vic.gov.au/infectious-diseases/information-for-the-public-japanese-encephalitis-in-victoria>

<https://www.betterhealth.vic.gov.au/japanese-encephalitis>

APPENDIX E: INSIGHT+ NEWS PUBLICATION

Available online at: <https://insightplus.mja.com.au/2023/36/re-emerging-flaviviruses-prompt-call-for-improved-detection/>

Re-emerging flaviviruses prompt call for improved detection

By Tilda Thomson, Madeleine Marsland, Maxwell Braddick, Helen O'Brien

In early 2022, the flavivirus Japanese encephalitis virus (JEV) unexpectedly [caused an outbreak](#) of encephalitis in humans and porcine stillbirths in [piggeries in south-eastern Australia](#).

The virus had caused a handful of sporadic cases in the extreme north of the country in the preceding decades, but locally acquired cases in the southeast were completely unheard of and precipitated the declaration of a [Communicable Disease Incident of National Significance](#) by the Australian Government Department of Health and Aged Care.

Much [remains unknown](#) about the Australian ecology of JEV, which circulates [between water birds and mosquitoes](#) and can spill over to humans and other mammals. Although it was initially unclear whether JEV would re-emerge in the southeast following this outbreak, in late 2022 further cases were identified.

Later in 2022, significant flooding led to increasing numbers of water birds and mosquitoes and provided favourable conditions for mosquito-borne disease outbreaks; and, by early 2023, another flavivirus outbreak began, with the [first human cases](#) of Murray Valley encephalitis detected in Victoria since 2011. Accompanying this, the related West Nile virus Kunjin subtype (KUNV) was [detected in mosquitoes](#), but no human cases were identified.

Suddenly, Australia faced an unprecedented situation with three encephalitic flaviviruses circulating during the mosquito season.

Although [most infections with these viruses are asymptomatic](#), for people who have encephalitis ([less than 1%](#)), the consequences are severe. Death occurs in up to [30% of cases](#), and between [30% and 50%](#) experience long term sequelae, including neurological, cognitive or psychiatric deficits. Despite KUNV infection being [slightly less severe](#) than JEV and Murray Valley encephalitis virus (MVEV) infections, in practice it is not possible to differentiate between the viruses clinically. [Effective use of laboratory diagnostics](#) in a case of encephalitis is challenged by serological cross-reactivity and polymerase chain reaction (PCR) methods, which, although highly specific, are relatively insensitive in the setting of brief viraemia.

Over the past two years, Australia has recorded [45 cases](#) of Japanese encephalitis and [26 cases of Murray Valley encephalitis](#), with a total of 16 deaths ([Victoria](#), [Northern Territory](#), [Western Australia](#)).

What did we do?

In response to the JEV outbreak, a [targeted vaccination campaign](#) was implemented. Initially the Australian Government's vaccine supply was limited and jurisdictions needed to prioritise populations who were at greatest risk of infection.

Now there is greater availability of JEV vaccine and an opportunity to vaccinate people in high risk regions to minimise the impact of future outbreaks.

Cases of JEV infection that present to health care represent the tip of the epidemiological iceberg, with asymptomatic infections and many milder presentations likely going undiagnosed. To measure the extent of the outbreak, we supported a [national serosurveillance program](#) to better understand the distribution of and risk factors for JEV infection to inform our prevention and preparedness strategies ahead of future mosquito seasons.

Serosurveys conducted throughout late 2022 found that 3% of the [northern Victoria](#) population and one in 11 people across [five towns in New South Wales](#) had evidence of prior JEV infection. For global context, a serosurvey of [unvaccinated adults in Kerala, India](#), where JEV is endemic, returned a seroprevalence of 16%.

The Australian serosurveys show that a large number of people were likely infected within a short time period, but, most importantly, that the majority of unvaccinated people do not have immunity from prior infection and, consequently, remain vulnerable to future infection.

Even though vaccines will support us to reduce the risk of JEV infection, there are no vaccines currently available for MVEV or KUNV.

Consequently, prevention relies on interrupting the interface between mosquitoes and humans. Governments have deployed multilevel strategies to protect at-risk communities from mosquito exposure, including bite-prevention education campaigns and integrated mosquito control programs. These strategies are dynamic and can respond to signals from early warning surveillance systems, such as [trapping mosquitoes and testing for viruses with PCR](#), before spillover to humans occurs.

What happens next?

Often, in health, we hope for the best but prepare for the worst.

Looking back, the historic pattern of MVEV in Australia is underscored by sporadic cases in the north of the country interspersed with significant south-eastern outbreaks, often separated by many decades. The historic dataset for JEV in mainland Australia includes only two mosquito seasons, with back-to-back cases.

The future remains uncertain. JEV may settle into a pattern similar to MVEV, with sporadic cases and infrequent outbreaks. Despite considerable uncertainty, the abundance of animal hosts and capable vectors throughout Australia means that preparing for the long term persistence of the virus should be a priority.

However, the climate is changing and [flood events are likely to increase](#) in frequency and intensity. The final impact of these changes on the complex ecological relationship between mosquitoes, water birds, humans and viruses is yet to be determined. Globally, mosquito-borne diseases are on the move, with the dengue-carrying *Aedes* mosquitoes [spreading in southern Europe](#) and [locally acquired cases of malaria detected](#) in Florida and Texas, prompting tough questions on the role of a warming climate in these instances of disease spread.

The place-based names of these flaviviruses do not accurately describe their broad geographic potential, and there are hard-learned lessons of unexpected spread. In 1999, West Nile virus (WNV) was detected in the United States for the first time. Within three years, the reach of the [virus had rapidly expanded](#) from one state to being widely spread across the United States. The [virus is now endemic](#) in North America, with thousands of cases reported annually and millions of people having been infected over the past 20 years.

[WNV causes less severe clinical illness than JEV and MVEV](#), but the viruses and their vectors are closely related. The recent history of MVEV demonstrates the potential for flaviviruses to rapidly expand, become endemic, and continue to cause substantial morbidity and mortality on an annual basis.

In a worst case but very plausible scenario, the recent emergence of JEV in Australia may only be the first step. There may be an ecological niche for JEV beyond the boundaries of the 2022 outbreak. The population is largely [immunologically naïve](#) to these viruses, and there is a potential for substantial disease and death to occur if this risk is not managed.

What do we need to do?

Vaccination, surveillance, prevention.

There is a need to invest in our mosquito and flavivirus surveillance to support rapid detection during mosquito seasons, ideally before we see human cases.

We also need to support the population to be aware of the risks from these flaviviruses, and to take action to protect themselves and others. This includes taking actions to avoid being bitten by mosquitos, such as [applying repellent, limiting outdoor activity when mosquitoes are about, and covering up when outdoors](#).

All of these viruses are preventable. For JEV, with sufficient vaccine supply now available to meet demand for eligible groups, there is an opportunity for wide vaccination coverage in at risk areas. It is recommended that people aged two months and older living in high risk areas get vaccinated.

For all flaviviruses, protection from mosquito bites prevents infection. Clinicians have a key role as advocates in our health care system, and should actively consider who might be at risk and encourage vaccination and preventive actions.

There remain many unknowns. We don't yet have enough evidence to fully understand where these viruses are most likely to emerge or who is at greatest risk. We don't know how long the vaccine protects against JEV, or whether it may offer protection against other flaviviruses. We also don't know if, as the climate changes, other mosquito-borne diseases, such as dengue or malaria, may enter and spread through parts of Australia.

Research is the cornerstone of effective evidence-based policy. Further work is needed to support our response, including a better understanding of what has happened in these recent outbreaks. Victoria will shortly commence an MVEV serosurvey in northern Victoria. We welcome the support of the medical community in recruiting for this important research.

Tilda Thomson is a Master of Philosophy in Applied Epidemiology (MAE) scholar at the Victorian Department of Health.

Dr Madeleine Marsland is a Master of Philosophy in Applied Epidemiology (MAE) scholar at the Victorian Department of Health.

Dr Maxwell Braddick is an infectious diseases physician and medical epidemiologist at the Victorian Department of Health, and the Royal Melbourne Hospital's Victorian Infectious Diseases Service.

Dr Helen O'Brien is a public health physician and Senior Medical Adviser in communicable diseases at the Victorian Department of Health.

APPENDIX F: MANUSCRIPT ACCEPTED FOR PUBLICATION

Serosurvey for Japanese encephalitis virus and related flaviviruses following an outbreak in an immunologically naïve population, Victoria, Australia

Authors

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¹ These first authors contributed equally to this article.

Abstract

Objectives: To investigate the distribution and prevalence of Japanese encephalitis virus (JEV) infection in northern Victoria following the 2022 outbreak, identify groups who may be at higher risk of infection, and investigate related flaviviruses (Murray Valley encephalitis virus (MVEV) and West Nile virus Kunjin subtype (WNVKUN)).

Design: Cross-sectional serosurvey with recruitment between 8 August and 1 December 2022.

Setting: Recruitment at pathology collection centres across three Local Public Health Unit catchment areas in northern Victoria – Ovens Murray, Goulburn Valley, and Loddon Mallee.

Participants: 813 participants were recruited. Individuals were excluded from participating if they had previously been vaccinated against or diagnosed with Japanese encephalitis, or were born in a country where JEV is endemic.

Main outcome measures: Seroprevalence and prevalence odds ratios (POR) for investigated risk factors.

Results: In total, 27 of 813 (3.3%, 95% confidence interval (CI) 2.2–4.8%) participants were JEV seropositive (IgG positive and IgM negative, suggesting past infection). JEV seropositive participants were detected at all recruitment locations, including locations where clinical cases had not been identified. Most investigated risk factors were not statistically associated with JEV infection, aside from older age (POR=1.1, 95% CI 1.0–1.1, $p<0.001$) and exposure to feral pigs (POR 20.9, 95% CI 1.7–188.1, $p=0.01$). MVEV and WNVKUNV seroprevalence was 3.0% (23/760) and 3.3% (25/761), respectively.

Conclusions: These results suggest ongoing population vulnerability to JEV remains in northern Victoria and that there are few consistent risk factors associated with infection. Additional prevention strategies including expansions of vaccine eligibility criteria may be required.

Summary box

The known: The Victorian population was largely considered immunologically naïve to Japanese encephalitis virus (JEV) prior to the 2022 outbreak. Most infections are asymptomatic making it difficult to detect the true prevalence of infection.

The new: We found evidence of JEV infection across northern Victoria including in areas where there had been no human cases of Japanese encephalitis. Our findings suggest ongoing population vulnerability to infection, with few risk factors statistically associated with infection.

The implications: It remains uncertain whether JEV will become endemic to the region. Expanded vaccine eligibility criteria may be required to protect against infection.

Introduction

Japanese encephalitis virus (JEV) is a zoonotic mosquito-transmitted flavivirus [1]. Water birds maintain and amplify the virus in the environment, and pigs are important amplifying hosts for transmission to humans, which primarily occurs via *Culex* mosquitoes [2]. Whilst the majority of JEV infections are asymptomatic, approximately 0.1% to 1% result in Japanese encephalitis (JE), a life-threatening illness [1, 3]. Of all flaviviruses, JEV is notable for causing significant morbidity and mortality in endemic regions across South-East Asia and the Western Pacific [4]. The case fatality rate among those who develop encephalitis is between 20% and 30% [1, 3], and between 30% and 50% of encephalitis cases experience long-term neurological sequelae [1, 3, 5].

The first outbreak of JE in south-eastern Australia occurred in 2022, following detection of JEV in piggeries in February and targeted investigation of human encephalitis cases in March across Victoria, New South Wales (NSW), Queensland and South Australia [6, 7]. Following these human case detections, the JEV outbreak was declared a Communicable Disease Incident of National Significance [8]. In the initial outbreak, a total of 42 human cases (32 confirmed and 10 probable) were reported nationally, of which 13 were Victorian residents [8, 9]. Given the low ratio of clinical to subclinical cases (estimates range from 1:25 to 1:1000) [2], it is thought that thousands of undetected JEV infections likely occurred nationally as part of this outbreak [6, 10, 11].

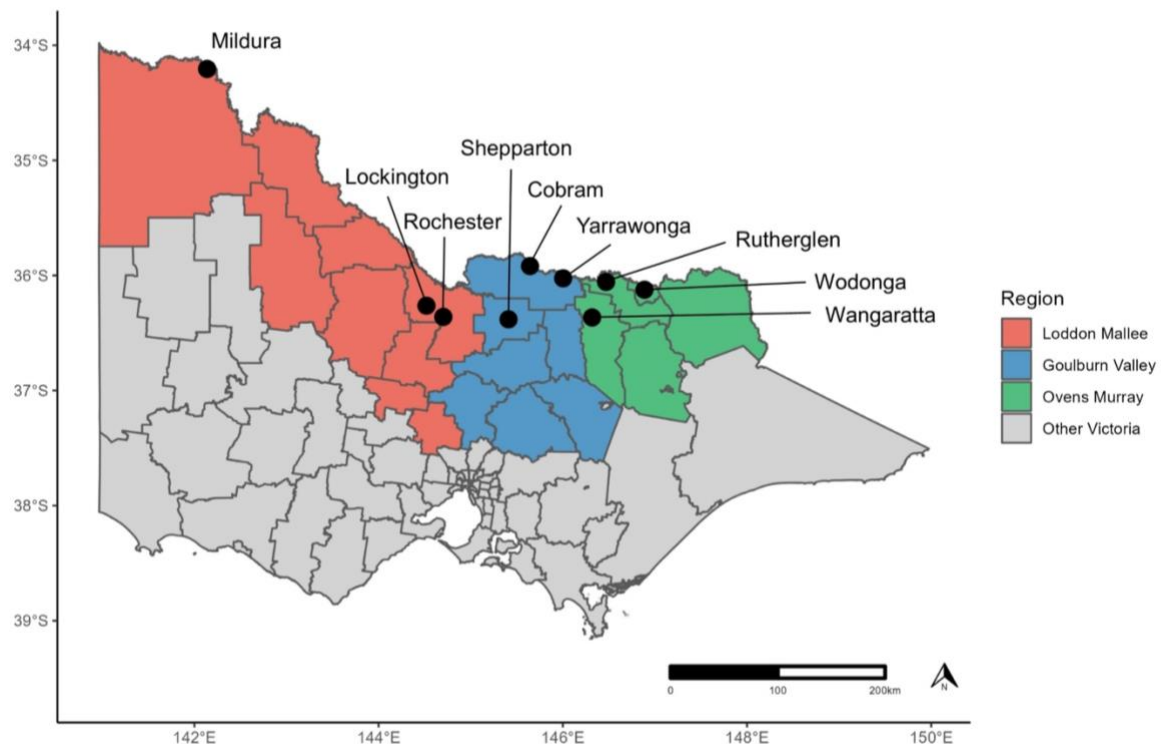
As part of the initial outbreak response in March 2022, Australia prioritised select population groups for vaccination [11, 12]. However, to guide prevention strategies, including a wider vaccination program, further characterisation of those most at risk of JEV infection was required. Within this context, we sought to investigate the distribution and prevalence of JEV infection in northern Victoria following the outbreak and identify groups of people who may be at higher risk of infection within these communities.

The closely related Murray Valley encephalitis virus (MVEV) and West Nile virus Kunjin subtype (WNVKUN) are endemic to Australia, with MVEV outbreaks occurring in southern Australia in 1951, 1974 and 2011, though no human cases were reported in Victoria in 2011 [13]. Following the detection of MVEV and WNVKUN in Victoria in early 2023 [14], additional retrospective testing was conducted on serosurvey samples to support the interpretation of serological results, assess seroprevalence, and inform public health actions.

Methods

This study was part of a national JEV serosurveillance program (Winkler et al, BMJ in press). Recruitment occurred from 8 August to 1 December 2022. Primary recruitment locations were across 3 Victorian Local Public Health Unit catchment areas – Ovens Murray, Goulburn Valley, and Loddon Mallee (Figure 1) – and were selected as areas considered to be at high risk of JEV infection, based on locations of exposure for known JE cases, infected piggeries, and JEV-positive mosquito detections during the 2022 outbreak.

Figure 1: Primary recruitment locations for Japanese encephalitis virus and related flaviviruses serosurvey, Victoria, Australia, 2022



Individuals were excluded from participating if they had previously been diagnosed with or vaccinated against JE, or were born in a country where JEV is known to be endemic (Bangladesh, Brunei, Burma, Cambodia, China, Guam, India, Indonesia, Japan, Laos, Malaysia, Nepal, North Korea, Pakistan, Papua New Guinea, Philippines, Russia, Saipan, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, Timor-Leste, Vietnam).

We used multiple recruitment strategies including:

- Opportunistic recruitment: participants having routine blood collections at a participating pathology centre.
- Targeted recruitment: groups who may be underrepresented in opportunistic recruitment (e.g., younger males who are less likely to attend for routine blood collections), through outreach (e.g., phone calls, emails, or meetings with community groups) and advertisements (via radio, newspapers, and social media).

Participants provided informed consent via an online form, with parent or guardian consent required for those aged under 18 years. They completed an online questionnaire regarding potential exposures and risk factors and had a blood sample collected. Participants who were found to be seropositive completed a follow-up telephone questionnaire with investigators to confirm responses provided in the online questionnaire and provide additional risk factor information and potential exposure locations.

All participants were tested for JEV IgM and IgG antibodies at the Victorian Infectious Diseases Reference Laboratory (VIDRL) using an Euroimmun immunofluorescence assay (IFA) as a screening test, performed in accordance with manufacturer's instructions [15, 16]. This assay targets the JEV genotype I envelope protein (M28 strain, taxid:2555554). Where a participant tested positive, additional testing was conducted for other closely related flaviviruses to assess for cross-reactivity (Dengue virus IgM and IgG using an enzyme-linked immunosorbent assay (ELISA), MVEV total antibody, WNVKUN total antibody and JEV total antibody using in-house developed defined epitope blocking (DEB) ELISA), as described and validated by Kinsella et al [17]. Samples were also sent for

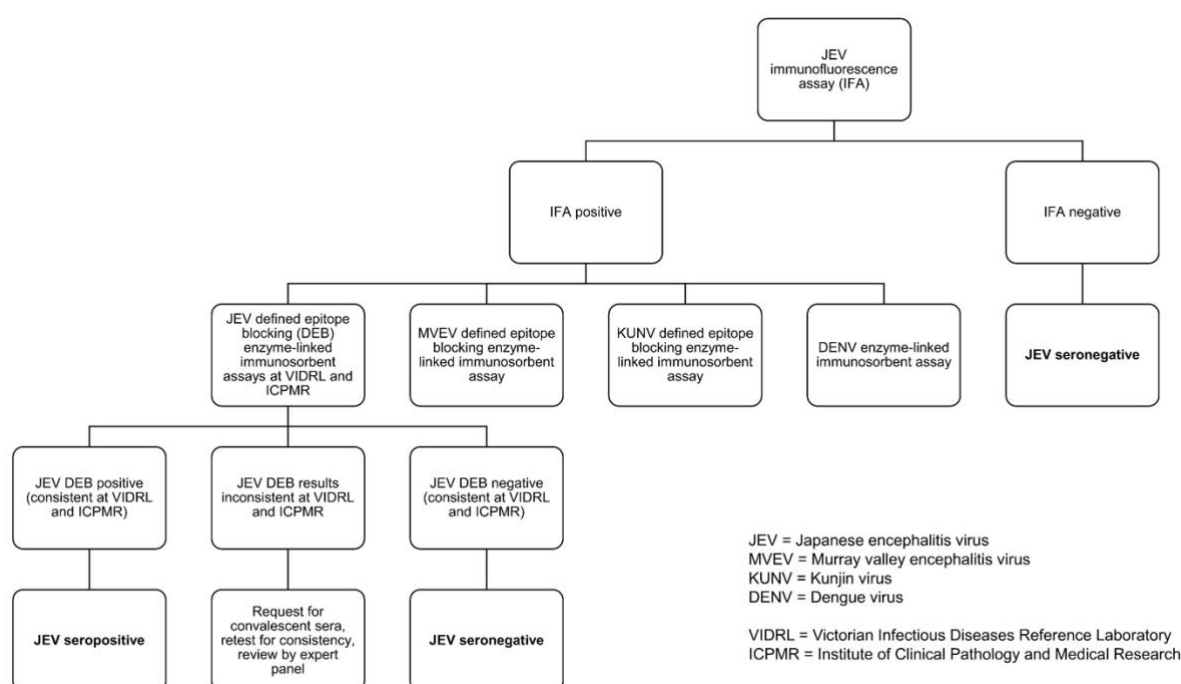
parallel testing for JEV total antibody using an in-house DEB ELISA [18] at the Institute of Clinical Pathology and Medical Research (ICPMR) in NSW. An Expert Review Panel (ERP) reviewed serological results from all assays alongside questionnaire responses for all participants who tested positive via IFA at VIDRL and classified them ‘seropositive’ if they had evidence of prior JEV infection (i.e., JEV IgG positive and total antibody positive) and ‘seronegative’ if there was insufficient evidence (i.e., JEV total antibody negative or inconsistent results suggesting a false positive on one assay). Where requested by the ERP, participants were contacted to have an additional blood sample collected and tested to support interpretation of results, provided they had not been vaccinated for JEV following recruitment (Figure 2). Samples from JEV seronegative participants with sufficient volume remaining were retrospectively tested for MVEV and WNVKUNV at VIDRL using in-house DEB ELISAs.

The primary outcome was JEV IgG seroprevalence for the sample as a whole and stratified by exposures of interest. Secondary outcomes were MVEV and WNVKUNV seroprevalence. Results were descriptively analysed, prevalence odds ratios (PORs) for exposures of interest were calculated, and confidence intervals (CI) and p-values were derived using Fisher’s exact test for categorical predictor variables, with age assessed as a continuous predictor variable using logistic regression.

Statistical analyses were undertaken using Stata version 16. Maps were produced in R version 4.1.2.

Ethical approval was received from the Sydney Children’s Hospital Network Human Research Ethics Committee (protocol 2022/ETH01167). Our report conforms with relevant guidelines (Appendix 1).

Figure 2: Testing algorithm to determine Japanese encephalitis virus seropositivity



Results

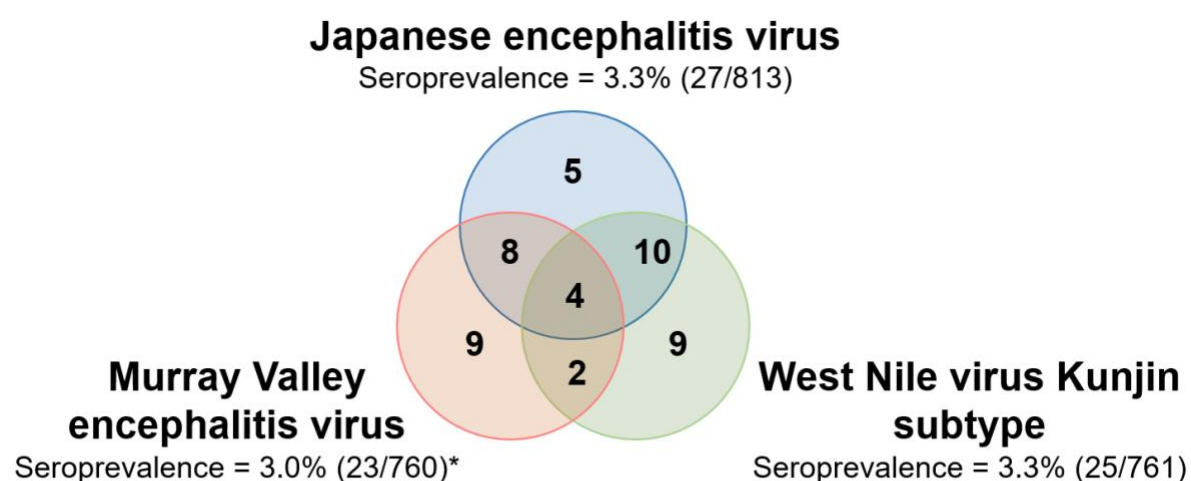
A total of 813 participants were recruited, of whom 27 (3.3%, 95% CI 2.2–4.8%) had evidence of prior JEV infection. No samples suggested recent JEV infection (i.e., confirmed IgM positive). Twenty-three of 27 JEV seropositive participants completed a follow-up questionnaire, with 4 participants lost to follow-up.

Of these 27 JEV seropositive participants, 8 tested positive for MVEV total antibody, 10 tested positive for WNVKUN total antibody, and 4 tested positive for all three flaviviruses, with 5 positive for JEV total antibody only.

Among JEV seronegative participants, 761 of 786 (96.8%) had sufficient sample remaining for further testing. Nine samples tested positive for MVEV total antibody, 9 tested positive for WNVKUN total antibody and 2 tested positive for both MVEV and WNVKUN total antibody (Figure 3). The overall MVEV seroprevalence was 3.0% (23/760, 95% CI 1.9–4.5%) and the WNVKUNV seroprevalence was 3.3% (25/761, 95% CI 2.1–4.8%).

Recruitment varied substantially by region and recruitment location, with 555 participants recruited in the Ovens Murray region, 195 in Goulburn Valley and 63 in Loddon Mallee. By recruitment method, 20 of 660 (3.0%) opportunistic recruits were JEV seropositive compared with 7 of 153 (4.6%) targeted recruits. This difference was not statistically significant ($p=0.32$).

Figure 3: Results of serological testing of serosurvey samples for Japanese encephalitis virus, Murray Valley encephalitis virus and West Nile virus Kunjin subtype



* One equivocal result excluded

Demographic factors

Demographics are reported in Table 1. All JEV seropositive participants were born in Australia, and most (16/27) reported they had never travelled to a JEV endemic country, with 6 (of 23 who answered this question in the follow-up questionnaire) reporting travel to an endemic region for >1 month.

The median age of participants was 59 years (range 7 to 92 years), and the median age of JEV seropositive participants was 73 years (range 25 to 90 years). PORs showed a statistically significant association between age and prior infection for all 3 flaviviruses, with the odds of infection increasing by 1.1 (95% CI 1.0–1.1, $p<0.001$), 1.0 (95% CI 1.0–1.1, $p=0.012$) and 1.1 (95% CI 1.0–1.1, $p<0.001$) per year of age for JEV, MVEV and WNVKUN, respectively.

While 61.0% (496/813) of participants were female, approximately half (14/27) of JEV seropositive participants were male (Table 2). However, no statistically significant difference in the odds of JEV, MVEV or WNVKUN infection between males and females was found.

Table 1: Demographics and flavivirus seroprevalence

Demographic factors	Primary serosurvey testing		Secondary testing of residual samples			
	JEV* positive, no. (%)	Number of participants	MVEV† positive, no. (%)	Number of participants	WNVKUN‡ positive, no. (%)	Number of participants
Age (years)						
0-9	0 (0%)	1	0 (0%)	1	0 (0%)	1
10-19	0 (0%)	21	0 (0%)	19	0 (0%)	19
20-29	1 (2%)	64	3 (5%)	62	0 (0%)	62
30-39	1 (1%)	104	1 (1%)	95	0 (0%)	95
40-49	0 (0%)	90	0 (0%)	88	0 (0%)	88
50-59	3 (2%)	134	2 (2%)	129	2 (2%)	130
60-69	5 (2%)	202	3 (2%)	184	9 (5%)	184
70-79	11 (7%)	151	9 (6%)	139	9 (6%)	139
80+	6 (13%)	46	5 (12%)	43	5 (12%)	43
Sex						
Male	14 (4%)	317	10 (3%)	291	14 (5%)	291
Female	13 (3%)	496	13 (3%)	469	11 (2%)	470
Aboriginal and Torres strait islander descent						
Not Aboriginal or Torres Strait Islander	25 (3%)	782	22 (3%)	731	22 (3%)	732
Aboriginal	1 (8%)	13	1 (8%)	13	2 (15%)	13
Torres Strait Islander	0 (0%)	1	0 (0%)	1	0 (0%)	1
Prefer not to say	1 (6%)	17	0 (0%)	15	1 (7%)	15
Country of birth						
Australia	27 (4%)	740	22 (3%)	691	25 (4%)	692
Other non JEV* endemic country	0 (0%)	73	1 (2%)	69	0 (0%)	69
Total	27 (3%)	813	23 (3%)	760#	25 (3%)	761

* Japanese encephalitis virus (JEV)

† Murray Valley encephalitis virus (MVEV)

‡ West Nile virus Kunjin subtype (WNVKUN)

Excludes one sample with an equivocal result

Table 2: Japanese encephalitis virus seroprevalence by age and sex (n=813)

Age (years)	Male			Female		
	JEV* positive, no.	Total, no.	JEV* positive, % (95% CI†, %)	JEV* positive, no.	Total, no.	JEV* positive, % (95% CI†, %)
0-9	0	1	0% (0-98%)	0	0	-
10-19	0	7	0% (0-41%)	0	14	0% (0-23%)
20-29	0	11	0% (0-28%)	1	53	2% (0-10%)
30-39	0	24	0% (0-14%)	1	80	1% (0-7%)
40-49	0	35	0% (0-10%)	0	55	0% (0-6%)
50-59	0	51	0% (0-7%)	3	83	4% (1-10%)
60-69	3	86	3% (1-10%)	2	116	2% (0-6%)
70-79	7	80	9% (4-17%)	4	71	6% (2-14%)
80+	4	22	18% (5-40%)	2	24	8% (1-27%)
Total	14	317	4% (2-7%)	13	496	3% (1-4%)

* Japanese encephalitis virus (JEV)

† Confidence interval (CI)

Geographic factors

Most participants resided in the regions where recruitment occurred (766/813, 94.2%) and within close vicinity of the primary recruitment locations (Figure 4). JEV seroprevalence was highest for those living in Loddon Mallee (5/59) and lowest among those living in Ovens Murray (14/518, 2.7%) (Table 3). Generally, JEV seroprevalence was higher in north-west local government areas (LGAs) and lower in the north-east LGAs of Victoria (Figure 5). LGAs with JEV seropositive participants tended to be closer to the Murray River and the border of Victoria and NSW, with seroprevalence lower (or zero) in the more southerly LGAs. Sixteen LGAs had no JEV seropositive participants, however these LGAs also had fewer participants recruited (Table 4).

Similarly, evidence of prior MVEV and WNVKUN infection was detected across northern Victoria (Figure 6), with seroprevalence highest among those living in the Loddon Mallee region (4/46 and 3/46, respectively).

Figure 4: Postcodes where Japanese encephalitis virus (JEV) seropositive participants were identified and number of participants by residential postcode, Australia, 2022 (n=813)

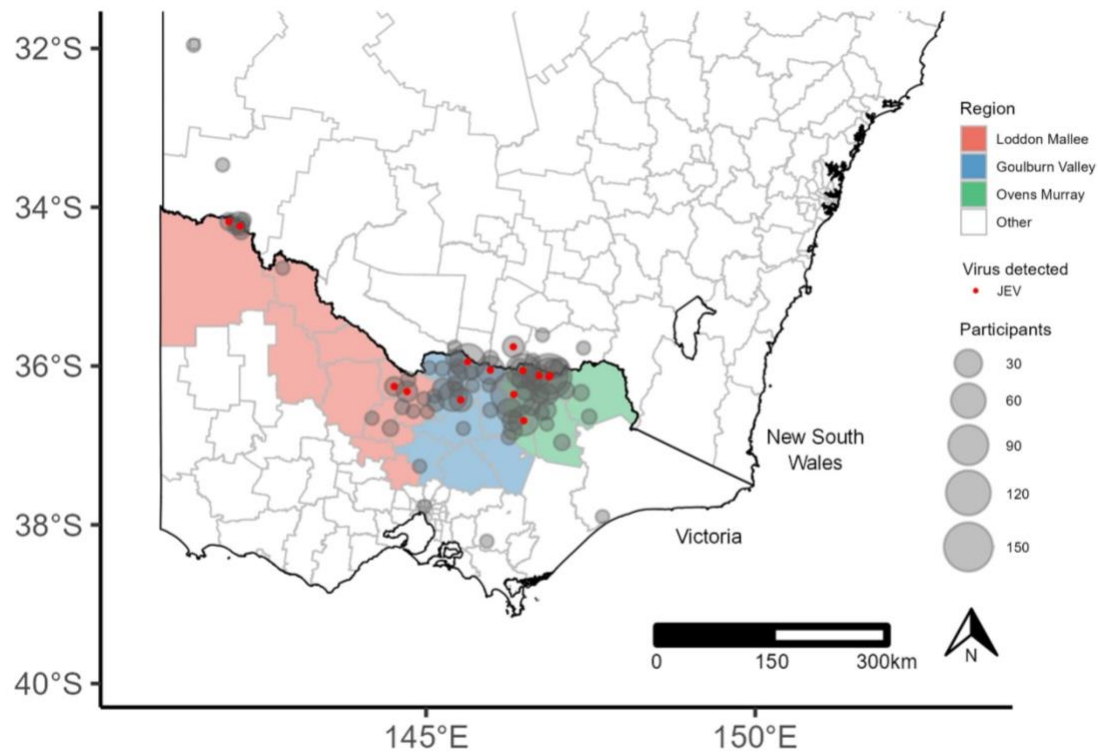


Figure 5: Japanese encephalitis virus seroprevalence by residential local government area, Australia, 2022 (n=813)

Local government area (LGA) labels: 1. City of Broken Hill, 2. Wentworth Shire, 3. Rural City of Mildura, 4. Rural City of Swan Hill, 5. Shire of Campaspe, 6. City of Greater Bendigo, 7. Shire of Mitchell, 8. City of Merri-bek, 9. Berrigan Shire, 10. Shire of Moira, 11. City of Greater Shepparton, 12. Shire of Strathbogie, 13. Federation Council, 14. Rural City of Benalla, 15. Rural City of Wangaratta, 16. Shire of Mansfield, 17. Shire of Baw Baw, 18. Greater Hume Shire, 19. City of Albury, 20. City of Wodonga, 21. Shire of Indigo, 22. Alpine Shire 23. Shire of Towong, 24. Shire of East Gippsland.

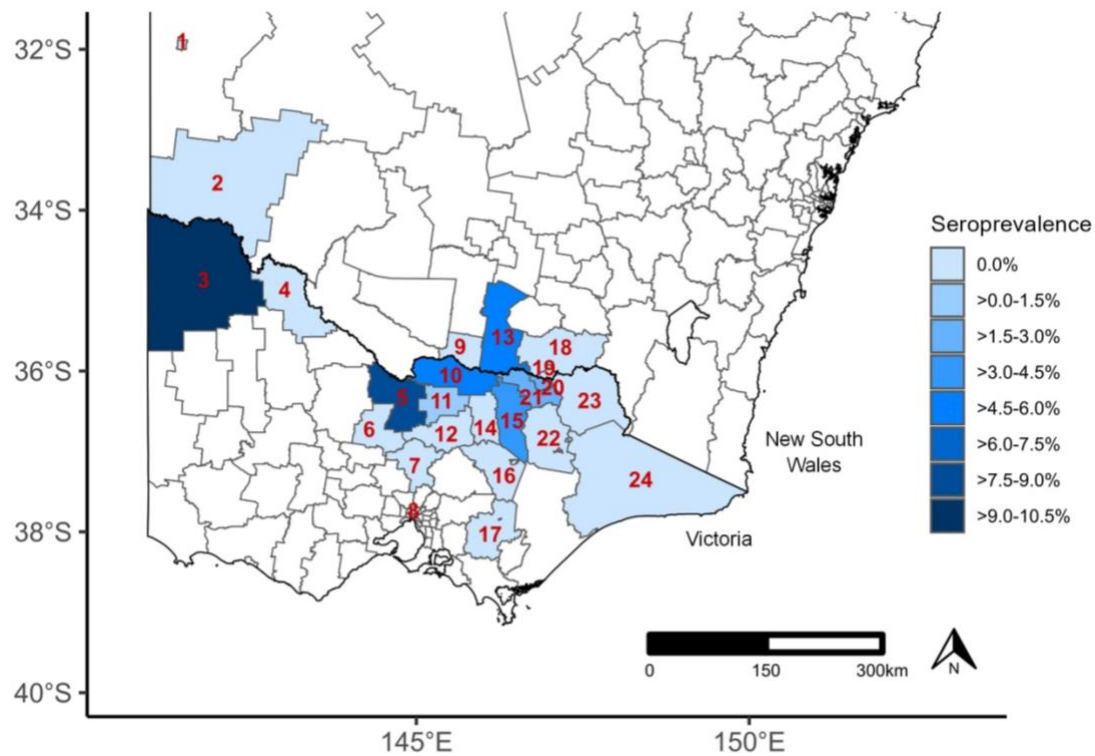


Figure 6: Postcodes where Murray Valley encephalitis virus (MVEV) and West Nile virus Kunjin subtype (WNVKUN) seropositive participants were identified, and number of participants by residential postcode, Australia, 2022 (n=761)

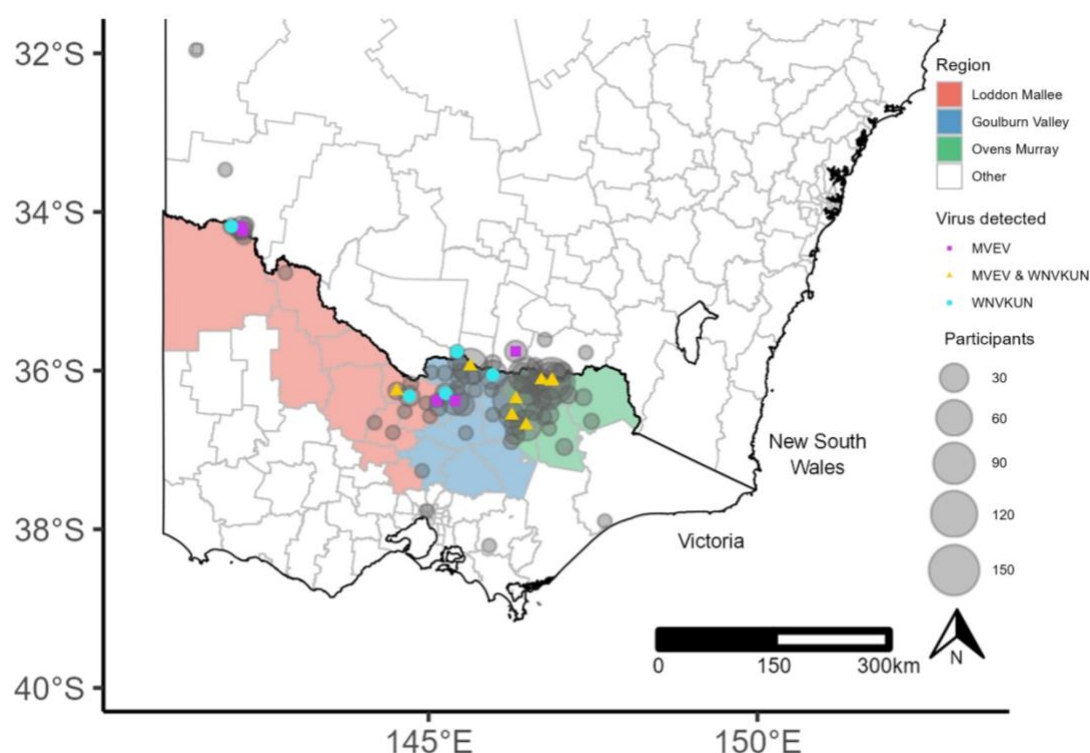


Table 3: Japanese encephalitis virus seroprevalence by residential region, for those living in investigated regions (n=766)

Residential region	JEV* positive, no.	Number of participants	JEV* positive, % (95% CI†, %)
Ovens Murray	14	518	3% (1–4%)
Goulburn Valley	7	189	4% (2–7%)
Loddon Mallee	5	59	8% (3–19%)
Total‡	26	766	3% (2–5%)

* Japanese encephalitis virus (JEV)

† Confidence interval (CI)

‡ One seropositive participant lived in a border community with a New South Wales address.

Table 4: Japanese encephalitis virus seroprevalence by residential local government area (n=813)

Residential local government area	JEV* positive, no. (%)	JEV* negative, no. (%)	Number of participants
Ovens Murray region			
Rural City of Wangaratta	7 (3%)	200 (97%)	207
City of Wodonga	5 (3%)	185 (97%)	190
Shire Indigo	2 (2%)	101 (98%)	103
Alpine Shire	0 (0%)	13 (100%)	13
Shire of Towong	0 (0%)	5 (100%)	5
Goulburn Valley region			
Shire of Moira	6 (6%)	102 (94%)	108
City of Greater Shepparton	1 (1%)	72 (99%)	73
Rural City of Benalla	0 (0%)	4 (100%)	4
Shire of Mansfield	0 (0%)	2 (100%)	2
Shire of Mitchell	0 (0%)	1 (100%)	1
Shire of Strathbogie	0 (0%)	1 (100%)	1
Loddon Mallee region			
Rural City of Mildura	3 (10%)	26 (90%)	29
Shire of Campaspe	2 (8%)	23 (92%)	25
City of Greater Bendigo	0 (0%)	4 (100%)	4
Rural City of Swan Hill	0 (0%)	1 (100%)	1
New South Wales			
Federation Council	1 (6%)	16 (94%)	17
City of Albury	0 (0%)	12 (100%)	12
Berrigan Shire	0 (0%)	8 (100%)	8
Greater Hume Shire	0 (0%)	3 (100%)	3
Wentworth Shire	0 (0%)	3 (100%)	3
City of Broken Hill	0 (0%)	1 (100%)	1
Other Victoria			
Shire of East Gippsland	0 (0%)	1 (100%)	1
Shire of Baw Baw	0 (0%)	1 (100%)	1
City of Merri-bek	0 (0%)	1 (100%)	1
Total	27 (3%)	786 (97%)	813

* Japanese encephalitis virus (JEV)

Exposure factors

JEV seropositive participants did not show significantly different odds of exposure to any of the investigated occupations, activities and locations, or the use of protective measures (Table 5). The only behavioural factor that increased the odds of JEV infection was exposure to feral pigs (POR 20.9, 95% CI 1.7–188.1, $p=0.01$). All participants with this exposure ($n=5$) reported they had infrequent contact with feral pigs (a few times a year).

Descriptive analysis showed JEV seropositive participants reported more frequent exposure to some risk factors than seronegative participants, such as daily exposure to mosquitoes and visiting farms at least a few times a month. However, these results were not statistically significant. When comparing outdoor exposures, there was no statistically significant difference in the time spent outdoors for work ($p=0.55$) or recreation ($p=0.84$), or time spent outdoors at dawn or dusk ($p=0.82$) between JEV seropositive and seronegative participants.

Similarly, very few risk factors were found to be associated with MVEV or WNVKUNV infection (Appendices 2–3).

Table 5: Univariable prevalence odds ratios of risk and protective factors for Japanese encephalitis virus infection (n=813)

Exposure variable	JEV* positive, no. (%)	JEV* negative, no. (%)	Prevalence odds ratio (95% CI) [†]
Occupation			
Abattoir or meat worker	0 (0%)	7 (1%)	0.0 (0.0–16.3)
Animal shooter or hunter	1 (4%)	19 (2%)	1.6 (0.0–10.6)
Council worker (Environmental Health Officer or outdoor staff)	0 (0%)	11 (1%)	0.0 (0.0–10.3)
Animal transport driver	1 (4%)	8 (1%)	3.7 (0.1–29.6)
Pig farmer or worker	0 (0%)	6 (1%)	0.0 (0.0–19.1)
Pest controller	1 (4%)	7 (1%)	4.3 (0.1–35.2)
Other type of farmer	7 (26%)	124 (16%)	1.9 (0.7–4.7)
Laboratory worker	0 (0%)	8 (1%)	0.0 (0.0–14.3)
Veterinarian	1 (4%)	1 (0%)	30.2 (0.4–2372.4)
Vet technician or nurse	0 (0%)	3 (0%)	0.0 (0.0–38.5)
Wildlife or zoo worker	0 (0%)	3 (0%)	0.0 (0.0–38.5)
Other outdoor occupation	1 (4%)	47 (6%)	0.6 (0.0–3.9)
Water exposure[#]			
Dams or lakes	14 (52%)	403 (51%)	1.0 (0.4–2.4)
Public or private pools	10 (37%)	314 (40%)	0.9 (0.4–2.1)
Irrigation systems	10 (37%)	242 (31%)	1.3 (0.5–3.1)
Wetlands	9 (33%)	271 (34%)	1.0 (0.4–2.3)
Rivers or creeks	19 (70%)	540 (69%)	1.1 (0.4–2.9)
Activities and locations[‡]			
Piggery [‡]	2 (7%)	29 (4%)	2.0 (0.2–8.9)
Abattoir	1 (4%)	15 (2%)	2.0 (0.1–13.8)
Agricultural show	4 (15%)	69 (9%)	1.8 (0.4–5.5)
Farm	14 (52%)	368 (47%)	1.2 (0.5–2.9)
States or National Parks	10 (37%)	368 (47%)	0.7 (0.3–1.6)
Camping	7 (26%)	285 (36%)	0.6 (0.2–1.5)
Fishing (fresh water)	6 (22%)	199 (25%)	0.8 (0.3–2.2)
Hunting	2 (7%)	36 (5%)	1.7 (0.2–7.1)
Bush walking or hiking	12 (44%)	353 (45%)	1.0 (0.4–2.3)
Water sports or boating	4 (15%)	182 (23%)	0.6 (0.1–1.7)
Gardening or horticulture	20 (74%)	611 (78%)	0.8 (0.3–2.3)
Picnicking	7 (26%)	254 (32%)	0.7 (0.3–1.8)
Outdoor sports	6 (22%)	259 (33%)	0.6 (0.2–1.5)
Animal exposure[§]			
Mosquitoes	20 (74%)	669 (85%)	0.5 (0.2–1.4)
Birds	13 (48%)	408 (52%)	0.9 (0.4–2.0)
Domestic pigs	0 (0%)	10 (1%)	0.0 (0.0–11.3)
Feral pigs	2 (7%)	3 (0%)	20.9 (1.7–188.1)
Horses	2 (7%)	113 (14%)	0.5 (0.1–2.0)
Bats	0 (0%)	41 (5%)	0.0 (0.0–2.6)
Protective factors			
Using mosquito repellent when outdoors	21 (78%)	613 (78%)	1.0 (0.4–3.0)
Using mosquito repellent when mosquitoes about	22 (81%)	693 (88%)	0.6 (0.2–2.1)
Wearing protective clothes outside in summer	25 (93%)	623 (79%)	3.3 (0.8–28.7)
Using mosquito preventing devices	15 (56%)	533 (68%)	0.6 (0.3–1.4)
Presence of insect screens at home	26 (96%)	776 (99%)	0.3 (0.0–15.1)

* Japanese encephalitis virus (JEV)

[†] Confidence interval (CI)

[#] Lived or worked in close proximity (within 5km) since 1 December 2021.

[‡] Visited location or participated in activity since 1 December 2021.

[‡] Lived or worked in close proximity (within 5km) since 1 December 2021, participants who answered “unsure” (n=50) were excluded from prevalence odds ratio calculations.

[§] Had exposure or close contact since 1 December 2021.

Discussion

This was the first serosurvey conducted to assess population exposure to JEV in Victoria. Similar to the results of other serosurveillance work conducted in NSW [19], our results suggest that many more people were infected with JEV in northern Victoria during the 2022 outbreak than was detected via case-based reporting. Conversely, our results suggest there continues to be population vulnerability to JEV, MVEV and WNVKUNV infection. This and other data on virus transmission from animal and vector studies highlights the need for an ongoing JEV vaccination program and the implementation of other prevention strategies to reduce the risk of human infection and clinical disease during future mosquito seasons, particularly as no vaccines are available for MVEV or WNVKUN.

We found evidence of JEV infection broadly across northern Victoria, including locations where JEV infection had only previously been detected in animals. Public messaging in the initial stages of the outbreak emphasised the risk of JEV along the Murray River and the border of Victoria and NSW. However, we also identified infection in those living in regional and rural towns further south. Our results support Victoria's progressive expansion of vaccine eligibility during the outbreak, with residents of high-risk LGAs initially prioritised and additional LGAs included as more supplies became available, but also highlight the complexities in quantifying risk based on the limited available surveillance data. The bird and mosquito species relevant for JEV transmission are widely distributed in Victoria and it is possible that the geographic range of the virus may expand in future seasons [20, 21]. A wider scale surveillance program could better determine the distribution of JEV in Victoria and identify changes in geographic risk, which may indicate the need for a more extensive vaccination program.

Children are at greatest risk of JEV infection in endemic countries, as most adults are exposed to infection during childhood [1, 22, 23]. However, this study and preliminary results from the NSW serosurvey [19] suggest that in this immunologically naïve population, older adults were most likely to be seropositive. Potential hypotheses to explain this association may include age related predilection to infection, differing exposures associated with age (e.g., occupational status and recreational activities), or the lifetime risk of exposure from prior travel. Older seropositive participants may have also been exposed to another related flavivirus, such as MVEV, in the past including during the large 1974 outbreak (given 25/27 of seropositive participants were aged ≥ 50 years), and our results may have been influenced by cross reactivity [24]. We also cannot exclude that JEV may have circulated undetected in south-eastern Australia in the past, leading to acquired immunity in older people [25], but no other evidence supports this. Whilst the cause of the association is unclear, it suggests that older adults are at greater risk of JEV infection, supporting Victoria's early policy decision, in the context of limited vaccine supply, to restrict JEV vaccination to adults ≥ 50 years. Whilst sex was not a statistically significant risk factor, prior research in endemic regions suggests males are more likely than females to be infected with JEV, experience clinical illness, and have poor outcomes [5, 22]. Given most JE cases in the initial outbreak were in older males [26], further investigation in immunologically naïve populations may be warranted.

Other than age, the only factor significantly associated with JEV infection was contact with feral pigs. However, as the number of participants reporting this exposure was small and their contact infrequent, further investigation is required to determine the strength of this association. Contact with domestic pigs was not significantly associated with JEV infection, although many piggery workers had already been vaccinated for JEV and were ineligible for our study. Animal surveillance in Victoria has focussed on domestic piggeries. JEV was detected in feral pigs in other Australian states and territories during the 2022 outbreak [7]. Expansion of current animal surveillance programs to include feral pigs could better define the risk associated with these animals.

Our serosurveillance detected lower JEV seroprevalence than in neighbouring NSW. This may reflect a true difference, with the risk of infection influenced by geographic variability. However, this difference could also be attributed to different testing methodologies (e.g., only samples positive on IFA at VIDRL were sent to ICPMR for testing) or differing recruitment strategies, with the NSW serosurvey solely utilising advertising and community outreach. We found a slightly lower seroprevalence among participants recruited opportunistically compared to through targeted

strategies, suggesting that self-selection bias may have influenced these results. Results from serosurveys in other Australian states and territories, and incorporation of all data together with other human case-based data, animal and vector surveillance data may shed further light on these differences across affected areas.

Our study had several limitations. As we aimed to rapidly understand risk factors for seroprevalence in the regional population where JEV cases were reported, no urban control population was used. The sample was skewed towards older age and female sex. Most participants were recruited opportunistically and may have had underlying medical conditions that influenced their risk, leading to the seroprevalence being over- or under- estimated. Participation was hampered in some areas due to extensive flooding in northern Victoria throughout October and November 2022. Recruitment at each location varied significantly and was influenced by the size and throughput of pathology centres, the availability of staff, and the opportunities for outreach activities. The variation in sample size in each region also likely influenced the overall estimated seroprevalence, particularly given seroprevalence was highest in the locations with the fewest participants. Some seropositive individuals may have acquired infection during prior travel (6 JEV seropositive individuals reported >1 month in endemic regions).

Whilst we utilised several assays to classify participants, the close antigenic relationship between flaviviruses presents difficulties for interpreting serological results [27]. Several participants were seropositive for multiple flaviviruses, which may reflect participants having had more than one prior flavivirus infection, or cross-reactivity. We used DEB assays with high specificity to improve the detection of specific flaviviruses, through utilisation of immunodominant epitopes on the proteins of JEV, MVEV and WNVKUN viruses and viral specific monoclonal antibodies [27]. Despite this, some participants may have been misclassified as seronegative or seropositive. JEV has rarely emerged in regions where MVEV is endemic, so there is limited evidence to understand the influence of cross-reactivity in this context [11, 28].

Of note, our results suggest evidence of prior MVEV infection among younger participants, specifically those aged 20–29 years, who could not have been infected during the 1974 outbreak. This suggests that either MVEV has continued circulating in Victoria in the absence of mosquito detections and detectable human outbreaks in recent years, or infections occurred during previous travel to more northern parts of the country. Within the context of these findings and the 2023 outbreak, there is a need to further investigate all flaviviruses and potential cross-reactivity. A serosurvey for MVEV in high-risk LGAs in regional Victoria is currently in progress [29].

Our study provides a greater understanding of the pattern and extent of JEV infection in northern Victoria following the recent outbreak and provides a foundation for further flavivirus research in this region. Our findings have implications for other populations across Australia and internationally, with the potential for JEV to emerge in other regions [30]. Given appropriate hosts and mosquito vectors are present, JEV will likely become established in year-round transmission cycles in northern Australia, with occasional extension into temperate regions when environmental conditions are suitable [31]. Our study provides useful evidence that supports vaccination recommendations in the context of limited supply and highlights the need for prevention strategies to protect the community. Our findings suggest there may be ongoing population vulnerability to JEV in Victoria, and with few consistent risk factors associated with infection, further expansions of vaccine eligibility criteria may be required to prevent future infections in Victoria and Australia.

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Appendices

Appendix 1: STROBE checklist

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 2: Univariable prevalence odds ratios of risk and protective factors for Murray Valley encephalitis virus (MVEV) infection (n=760)

Exposure variable	MVEV* positive, no. (%)	MVEV* negative, no. (%)	Prevalence odds ratio (95% CI†)
Occupation			
Abattoir or meat worker	0 (0%)	7 (1%)	0.0 (0.0–18.1)
Animal shooter or hunter	1 (4%)	17 (2%)	1.9 (0.0–13.4)
Council worker (Environmental Health Officer or outdoor staff)	0 (0%)	8 (1%)	0.0 (0.0–15.8)
Animal transport driver	2 (9%)	7 (1%)	9.9 (0.9–56.1)
Pig farmer or worker	0 (0%)	5 (1%)	0.0 (0.0–25.5)
Pest controller	0 (0%)	8 (1%)	0.0 (0.0–15.8)
Other type of farmer	6 (26%)	121 (16%)	1.8 (0.6–4.9)
Laboratory worker	0 (0%)	7 (1%)	0.0 (0.0–18.1)
Veterinarian	1 (4%)	1 (0%)	33.5 (0.4–2628.8)
Vet technician or nurse	0 (0%)	3 (0%)	0.0 (0.0–42.6)
Wildlife or zoo worker	1 (4%)	2 (0%)	16.7 (0.3–327.6)
Other outdoor occupation	1 (4%)	41 (6%)	0.8 (0.0–5.0)
Water exposure#			
Dams or lakes	13 (57%)	373 (51%)	1.3 (0.5–3.3)
Public or private pools	11 (48%)	289 (39%)	1.4 (0.6–3.6)
Irrigation systems	14 (61%)	215 (29%)	3.8 (1.5–10.0)
Wetlands	11 (48%)	249 (34%)	1.8 (0.7–4.5)
Rivers or creeks	16 (70%)	502 (68%)	1.1 (0.4–3.1)
Activities and locations*			
Piggery‡	1 (4%)	30 (4%)	1.0 (0.0–6.7)
Abattoir	1 (4%)	15 (2%)	2.2 (0.1–15.5)
Agricultural show	2 (9%)	61 (8%)	1.1 (0.1–4.5)
Farm	12 (52%)	344 (47%)	1.3 (0.5–3.2)
States or National Parks	8 (35%)	339 (46%)	0.6 (0.2–1.6)
Camping	5 (22%)	268 (36%)	0.5 (0.1–1.4)
Fishing (fresh water)	3 (13%)	192 (26%)	0.4 (0.1–1.5)
Hunting	3 (13%)	32 (4%)	3.3 (0.6–12.0)
Bush walking or hiking	11 (48%)	329 (45%)	1.1 (0.5–2.9)
Water sports or boating	2 (9%)	169 (23%)	0.3 (0.0–1.3)
Gardening or horticulture	18 (78%)	571 (77%)	1.1 (0.4–3.7)
Picnicking	8 (35%)	236 (32%)	1.1 (0.4–2.9)
Outdoor sports	3 (13%)	241 (33%)	0.3 (0.1–1.1)
Animal exposure§			
Mosquitoes	19 (83%)	620 (84%)	0.9 (0.3–3.7)
Birds	12 (52%)	384 (52%)	1.0 (0.4–2.5)
Domestic pigs	0 (0%)	9 (1%)	0.0 (0.0–14.0)
Feral pigs	0 (0%)	5 (1%)	0.0 (0.0–25.5)
Horses	3 (13%)	106 (14%)	0.9 (0.2–3.1)
Bats	2 (9%)	38 (5%)	1.8 (0.2–7.6)
Protective factors			
Using mosquito repellent when outdoors	15 (65%)	575 (78%)	0.5 (0.2–1.5)
Using mosquito repellent when mosquitoes about	16 (70%)	650 (88%)	0.3 (0.1–0.9)
Wearing protective clothes outside in summer	19 (83%)	587 (80%)	1.2 (0.4–5.0)
Using mosquito preventing devices	12 (52%)	500 (68%)	0.5 (0.2–1.3)
Presence of insect screens at home	22 (96%)	728 (99%)	0.3 (0.0–12.5)

* Murray Valley encephalitis virus (MVEV)

† Confidence interval (CI)

Lived or worked in close proximity (within 5km) since 1 December 2021.

♣ Visited location or participated in activity since 1 December 2021.

‡ Lived or worked in close proximity (within 5km) since 1 December 2021, participants who answered “unsure” (n=45) were excluded from prevalence odds ratio calculations.

§ Had exposure or close contact since 1 December 2021.

Appendix 3: Univariable prevalence odds ratios of risk and protective factors for West Nile virus Kunjin subtype (WNVKUN) infection (n=761)

Exposure variable	WNVKUN* positive, no. (%)	WNVKUN* negative, no. (%)	Prevalence odds ratio (95% CI) [†]
Occupation			
Abattoir or meat worker	0 (0%)	7 (1%)	0.0 (0.0–16.6)
Animal shooter or hunter	1 (4%)	17 (2%)	1.8 (0.0–12.2)
Council worker (Environmental Health Officer or outdoor staff)	0 (0%)	8 (1%)	0.0 (0.0–14.4)
Animal transport driver	2 (8%)	7 (1%)	9.1 (0.9–50.8)
Pig farmer or worker	0 (0%)	5 (1%)	0.0 (0.0–23.3)
Pest controller	1 (4%)	7 (1%)	4.3 (0.1–35.9)
Other type of farmer	6 (24%)	121 (16%)	1.6 (0.5–4.3)
Laboratory worker	0 (0%)	7 (1%)	0.0 (0.0–16.6)
Veterinarian	1 (4%)	1 (0%)	30.6 (0.4–2406.5)
Vet technician or nurse	0 (0%)	3 (0%)	0.0 (0.0–39.0)
Wildlife or zoo worker	0 (0%)	3 (0%)	0.0 (0.0–39.0)
Other outdoor occupation	0 (0%)	42 (6%)	0.0 (0.0–2.6)
Water exposure[#]			
Dams or lakes	15 (60%)	372 (51%)	1.5 (0.6–3.7)
Public or private pools	10 (40%)	291 (40%)	1.0 (0.4–2.5)
Irrigation systems	6 (24%)	223 (30%)	0.7 (0.2–1.9)
Wetlands	12 (48%)	248 (34%)	1.8 (0.7–4.4)
Rivers or creeks	17 (68%)	501 (68%)	1.0 (0.4–2.7)
Activities and locations[‡]			
Piggery [‡]	2 (8%)	29 (4%)	2.1 (0.2–9.1)
Abattoir	1 (4%)	15 (2%)	2.0 (0.1–14.1)
Agricultural show	2 (8%)	61 (8%)	1.0 (0.1–4.1)
Farm	11 (44%)	346 (47%)	0.9 (0.4–2.1)
States or National Parks	7 (28%)	340 (46%)	0.5 (0.2–1.2)
Camping	6 (24%)	267 (36%)	0.6 (0.2–1.5)
Fishing (fresh water)	5 (20%)	190 (26%)	0.7 (0.2–2.0)
Hunting	1 (4%)	34 (5%)	0.9 (0.0–5.6)
Bush walking or hiking	8 (32%)	332 (45%)	0.6 (0.2–1.4)
Water sports or boating	2 (8%)	169 (23%)	0.3 (0.0–1.2)
Gardening or horticulture	18 (72%)	572 (78%)	0.7 (0.3–2.1)
Picnicking	3 (12%)	241 (33%)	0.3 (0.1–1.0)
Outdoor sports	4 (16%)	240 (33%)	0.4 (0.1–1.2)
Animal exposure[§]			
Mosquitoes	22 (88%)	618 (84%)	1.4 (0.4–7.4)
Birds	18 (72%)	379 (52%)	2.4 (1.0–6.9)
Domestic pigs	0 (0%)	9 (1%)	0.0 (0.0–12.8)
Feral pigs	1 (4%)	4 (1%)	7.6 (0.6–80.4)
Horses	3 (12%)	106 (14%)	0.8 (0.2–2.8)
Bats	1 (4%)	39 (5%)	0.7 (0.0–4.8)
Protective factors			
Using mosquito repellent when outdoors	20 (80%)	571 (78%)	1.2 (0.4–4.0)
Using mosquito repellent when mosquitoes about	22 (88%)	645 (88%)	1.0 (0.3–5.5)
Wearing protective clothes outside in summer	22 (88%)	585 (80%)	1.9 (0.6–10.0)
Using mosquito preventing devices	16 (64%)	496 (67%)	0.9 (0.4–2.2)
Presence of insect screens at home	25 (100%)	726 (99%)	-

* West Nile virus Kunjin subtype (WNVKUN)

[†] Confidence interval (CI)

[#] Lived or worked in close proximity (within 5km) since 1 December 2021.

[‡] Visited location or participated in activity since 1 December 2021.

[‡] Lived or worked in close proximity (within 5km) since 1 December 2021, participants who answered “unsure” (n=45) were excluded from prevalence odds ratio calculations.

[§] Had exposure or close contact since 1 December 2021.

APPENDIX G: CONFERENCE PRESENTATIONS

Communicable Diseases & Immunisation Conference 2023

Demographic and behavioural risk factors for Japanese encephalitis virus (JEV) infection in Victoria

Madeline Marsland, Tilda Thomson, Helen O'Brien, Chuan Kok Lim, Rebecca Gang, Janet Strachan, Anna Glynn-Robinson, N. Deborah Friedman

Study rationale - First outbreak of Japanese Encephalitis (JE) in south-eastern Australia - Most JE cases are asymptomatic - Aim to understand extent of infection and risk factors to inform vaccination and prevention strategies Study design - Cross-sectional serosurvey in northern Victoria - Participants completed questionnaire and blood test Recruitment approaches - Opportunistic (routine bloods) n = 660 - Targeted (community outreach advertising) n=153 Analysis - Prevalence odds ratios of investigated exposures	Investigated exposures <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="background-color: #e6f2ff;"><i>Demographics</i></td> <td> ➤ Age and sex ➤ Country of birth, international travel ➤ Indigenous status </td> </tr> <tr> <td style="background-color: #e6f2ff;"><i>Occupation</i></td> <td> ➤ Outdoor (e.g. farmer, hunter, council) ➤ Animal contact (e.g. veterinarian, animal transport, wildlife, pests) </td> </tr> <tr> <td style="background-color: #e6f2ff;"><i>Water exposure</i></td> <td> ➤ E.g. Dams, pools, wetlands, rivers </td> </tr> <tr> <td style="background-color: #e6f2ff;"><i>Activities</i></td> <td> ➤ E.g. camping, fishing, hiking, gardening ➤ Time spent outdoors daily </td> </tr> <tr> <td style="background-color: #e6f2ff;"><i>Locations</i></td> <td> ➤ Outdoor (e.g. farm, national park) ➤ Animal contact (e.g. piggery, agricultural show, abattoir) </td> </tr> <tr> <td style="background-color: #e6f2ff;"><i>Animal contact</i></td> <td> ➤ E.g. mosquitoes, birds, pigs, horses </td> </tr> <tr> <td style="background-color: #e6f2ff;"><i>Protective factors</i></td> <td> ➤ Use of mosquito repellent ➤ Protective clothing ➤ Preventive devices </td> </tr> </table>	<i>Demographics</i>	➤ Age and sex ➤ Country of birth, international travel ➤ Indigenous status	<i>Occupation</i>	➤ Outdoor (e.g. farmer, hunter, council) ➤ Animal contact (e.g. veterinarian, animal transport, wildlife, pests)	<i>Water exposure</i>	➤ E.g. Dams, pools, wetlands, rivers	<i>Activities</i>	➤ E.g. camping, fishing, hiking, gardening ➤ Time spent outdoors daily	<i>Locations</i>	➤ Outdoor (e.g. farm, national park) ➤ Animal contact (e.g. piggery, agricultural show, abattoir)	<i>Animal contact</i>	➤ E.g. mosquitoes, birds, pigs, horses	<i>Protective factors</i>	➤ Use of mosquito repellent ➤ Protective clothing ➤ Preventive devices
<i>Demographics</i>	➤ Age and sex ➤ Country of birth, international travel ➤ Indigenous status														
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<i>Animal contact</i>	➤ E.g. mosquitoes, birds, pigs, horses														
<i>Protective factors</i>	➤ Use of mosquito repellent ➤ Protective clothing ➤ Preventive devices														

1

Key outcome: 3.3% (27/813) participants were JEV seropositive

Demographics of serosurvey participants Demographics of JEV seropositive participants	Key findings - Older age associated with JEV infection (POR=1.07, p<0.001) - Feral pig contact associated with JEV infection (POR=20.88, p=0.01) - No other investigated factors statistically associated - Sex not significantly associated - 51.9% of seropositive males ≥60 years - Of 27 positives - 2 sets of couples Limitations - Sample skewed towards older age and female sex - Potential-self-selection bias – seropositivity higher among targeted recruits (4.6%) vs opportunistic (3.0%) - Recruitment hampered due to flooding in some areas Key messages - Many people may have been exposed to JEV during outbreak - Widespread population vulnerability to infection remains - Few consistent risk factors among JEV infected persons - A population-wide vaccination strategy may be needed to reduce risk
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Acknowledgements: Department of Health, Victoria; Ovens Murray Public Health Unit; Goulburn Valley Public Health Unit; Victorian Infectious Diseases Reference Laboratory; National Centre for Immunisation Research and Surveillance; Australian National University
MM is a Master of Philosophy in Applied Epidemiology (MAE) scholar with the Australian National University and is supported by an MAE scholarship

2

SAFETYNET Scientific Conference 2023

Demographic and behavioural risk factors for Japanese encephalitis virus (JEV) infection in Victoria, Australia

Madeline Marsland, Tilda Thomson, Helen O'Brien, Chuan Kok Lim, Rebecca Gang, Janet Strachan, Anna Glynn-Robinson, N. Deborah Friedman



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1

Study rationale – Japanese encephalitis in Victoria

Rationale

- First outbreak of Japanese Encephalitis (JE) in south-eastern Australia
- Aim to understand:
 - Risk factors to inform vaccination and prevention strategies (Maddy)
 - Extent and distribution of infection (Tilda)

Study design

- Cross-sectional serosurvey in northern Victoria



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Study design – serosurvey in northern Victoria

Recruitment

- Opportunistic (routine bloods) n = 660
- Targeted (community outreach, advertising) n = 153

Analysis

- Prevalence odds ratios of investigated exposures

Investigated exposures

Category	Exposures
Demographics	Age and sex; Country of birth, international travel
Occupation	Outdoor (farmer, hunter, council); Animal contact (veterinarian, animal transport, wildlife, pests)
Water contact	Dams, pools, wetlands, rivers
Activities	Camping, fishing, hiking, gardening; Time outdoors
Locations	Outdoor (farm, national park); Animal contact
Animal contact	Mosquitoes, birds, pigs, horses
Protective factors	Use of mosquito repellent; Protective clothing & devices

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3

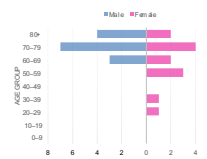
Key findings – demographics

- Key outcome: 3.3% (27/813) participants were JEV seropositive

Demographics of serosurvey participants



Demographics of JEV seropositive participants



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Key findings – investigated exposures



Credit: Agriculture Victoria

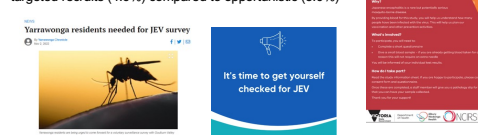
- Feral pig contact associated with JEV infection (POR=20.93, p<0.01)
- No other investigated factors statistically associated
- Of 27 positives – 2 sets of couples

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5

Limitations

- Sample skewed towards older age and female sex
- Potential self-selection bias – seropositivity higher among targeted recruits (4.6%) compared to opportunistic (3.0%)



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6

Key messages

- Many people have been exposed to JEV during outbreak
- Widespread population vulnerability to infection remains
- Few consistent risk factors among JEV infected persons
- A population-wide vaccination strategy may be needed to reduce risk

Up next = Distribution of infection and geographic risk

Acknowledgements: Department of Health, Victoria; Ovens Murray Public Health Unit; Goulburn Valley Public Health Unit; Victorian Infectious Diseases Reference Laboratory; National Centre for Immunisation Research and Surveillance; Australian National University
MM and TT are Master of Philosophy in Applied Epidemiology (MAE) scholars with the Australian National University and are supported by MAE scholarships

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CHAPTER IV

EVALUATION OF A SURVEILLANCE SYSTEM

Evaluation of the Australian Rotavirus Surveillance Program in
Victoria, Australia

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PROLOGUE

Study rationale

In late 2022, the Department of Health (DH) detected an unexpected increase in rotavirus cases occurring in Victoria. DH had commenced early discussions with the Murdoch Children's Research Institute (MCRI) about ways to become more actively involved with, and better utilise data from, the Australian Rotavirus Surveillance Program (ARSP). This evaluation is intended to support both the ARSP and DH to consider options to improve rotavirus surveillance in Victoria.

My role

I utilised the Centers for Disease Control and Prevention Updated Guidelines for Evaluating Public Health Surveillance Systems to conduct this evaluation [1]. In consultation with my supervisors and key informants from MCRI, I determined the scope of the evaluation, identified respondents, developed questionnaires and conducted interviews. MCRI provided me with de-identified aggregated data based on a data request I developed. DH provided me with de-identified line-listed data extracted from Victoria's Public Health Event Surveillance System (PHESS). I completed an analysis of the quantitative and qualitative data and developed the final evaluation report which has been presented to both DH and MCRI.

Lessons learned

This was the third project I attempted in order to meet the MAE competency of evaluating or establishing a surveillance system. From my earlier work, I had already developed some of the skills in questionnaire design and conducting interviews (see Chapter 7), which served me well as I rapidly undertook this project in 2023. There were several learnings from this project.

Firstly, I had very limited experience in program evaluation prior to this project and had never used a formal framework. Through this project, I learned about different frameworks, and how these are applied in different situations. I learned how to map out questions against each attribute relevant to the system under investigation, and how to prioritise my focus within a broad framework to get the most meaningful data for stakeholders.

This was the only project in my MAE where I used qualitative data. I had some previous experience analysing qualitative data but had never conducted my own interviews and analysed the data. I found this quite challenging, particularly as I had conducted semi-structured rather than structured interviews, and respondents often deviated from the questions and provided unexpected responses. Whilst most respondents were very helpful

and willing to participate, some interviews were particularly challenging to conduct and control, as respondents spoke quickly and could be very direct with their responses. Analysing this data also posed challenges, as there was a need to map responses back to the attributes, and there was often overlap and a lack of clarity regarding where things best fit.

Finally, it was important to me that this project was useful to both DH and MCRI, given they invested time and supported me to conduct this evaluation. In developing the report, I tried to consider actions that both stakeholders could take that would support each other to improve the ARSP, and by extension support rotavirus surveillance in Victoria. This is reflected in my recommendations, which are targeted at both the ARSP and DH.

Public health implications

The final report was shared with DH and MCRI, with stakeholders able to circulate it more broadly as they thought appropriate (such as with national funders of the ARSP). This evaluation supports a better understanding of the strengths and weaknesses of the ARSP in Victoria, and opportunities to improve the surveillance system. In particular, this evaluation would improve integration of the ARSP into PHESS to facilitate improved rotavirus surveillance in Victoria and linkage of results with other datasets. These lessons could also be applied at a national level.

Acknowledgements

Firstly, I would like to thank the team at MCRI, particularly Julie Bines, Sarah Thomas and Celeste Donato, for agreeing to this evaluation and providing invaluable support to me in collecting the necessary information and data (including allowing me to go an hour longer than scheduled during our interview!). I also thank all other respondents who participated in this evaluation for generously giving their time.

As always, I would like to thank my supervisors Anna Glynn-Robinson, Janet Strachan and Rebecca Gang who were instrumental in conducting this evaluation. I particularly acknowledge the extra work put in to help set up this project, given the program is run by the MCRI and required the buy-in of external stakeholders. I also would like to point out that as this was my third attempt at this competency, my supervisor team were involved in several proposals and work on other projects, and I thank them for supporting me in what at times felt like an exercise in frustration.

ABSTRACT

Introduction

The Australian Rotavirus Surveillance Program (ARSP) is a national surveillance system that characterises and genotypes rotavirus samples from across Australia. In late 2022, Victoria detected an unexpected increase in rotavirus notifications. Within this context, the Victorian Department of Health (DH) and the ARSP initiated this evaluation to consider opportunities to enhance surveillance of rotavirus and better integrate and utilise the ARSP in Victoria.

Methods

This evaluation was limited to Victoria and did not consider the broader national system. The Centers for Disease Control and Prevention (CDC) Updated Guidelines for Evaluating Public Health Surveillance Systems was used as a framework to investigate the attributes of the ARSP. Data on positive samples analysed by the ARSP were extracted from their database for the period 2012 to 2022, and data on rotavirus notifications received by DH were extracted from September 2018 when rotavirus became notifiable in Victoria to December 2022. Interviews and written feedback were sought from fifteen respondents across four groups (ARSP staff, DH staff, laboratories currently or previously collaborating, laboratories not collaborating), and eleven (73%) agreed to participate. Quantitative and qualitative data were descriptively analysed to develop recommendations.

Results

The ARSP is a relatively simple, acceptable and flexible system, with all respondents currently participating (4/4) willing to continue their involvement. The evaluation identified opportunities to improve recruitment and retention of collaborating laboratories, with several respondents (5/7) noting this was a key threat to the stability of the system. The evaluation highlighted weaknesses in the representativeness of the system, with notable discrepancies between the ARSP samples and DH rotavirus notifications in some geographical regions including south-west Melbourne and Greater Geelong. The evaluation also identified opportunities to better integrate the ARSP into DH systems, to provide results to collaborating laboratories to make the system more useful, and highlighted opportunities to improve the systems for investigating outbreaks in Victoria.

Discussion

The evaluation demonstrated that although the ARSP is a national system, it has the capacity to also support state-wide rotavirus surveillance. This evaluation supports a better understanding of the ARSP in Victoria, and highlights opportunities to both improve and

expand the program into the future. Although this evaluation focussed on the ARSP in Victoria only, the findings of this evaluation are likely to be relevant to the surveillance of rotavirus in other states and territories, and at the national level.

INTRODUCTION

Public health importance of rotavirus

Rotavirus is a highly transmissible RNA virus that belongs to the *Reoviridae* virus family and is primarily spread via the faecal-oral route [2-4]. Disease severity is variable and age dependent, with children aged <5 years and adults aged ≥70 years at greatest risk of severe disease [2, 3, 5, 6]. Symptoms are non-specific and typically involve gastroenteritis (i.e. vomiting and diarrhoea), which can result in dehydration and hospitalisation [3, 6, 7]. Elderly individuals are particularly at risk due to weakened immunity and comorbidities, and are often vulnerable to infection when residing in aged care facilities (ACFs) [5]. Outbreaks of rotavirus commonly occur in schools and childcare centres, as well as in ACFs [3]. Treatment is limited to supportive care and oral rehydration solutions [6].

Globally, rotavirus is a leading cause of diarrhoea-associated morbidity and mortality [2, 5]. The introduction of effective vaccination programs has led to a marked global reduction in rotavirus-associated deaths, from 659,053 in 1990 to 235,331 in 2019 [2, 5]. Mortality rates due to rotavirus have been historically low within Australia, with only 14 deaths listing rotavirus as the principal cause between 1990 and 2004 (approximately one per year) [8]. Death in Australia is now very rare due to the effective childhood vaccination program combined with universal health coverage [3, 9]. Within Australia, prior to the addition of rotavirus vaccines onto the National Immunisation Program (NIP), there were approximately 10,000 rotavirus-associated hospitalisations reported among children aged <5 years annually [3]. Rotavirus vaccines have been highly effective at reducing hospitalisations, and have remained relatively effective over time despite evidence of waning immunity with age [3, 9, 10]. There remain direct and indirect costs associated with rotavirus, however the vaccination program has been highly cost-effective in reducing hospitalisation by approximately 90% among children aged <5 years [6, 11]. Suboptimal vaccine effectiveness has been detected during some Australian outbreaks, including in the Aboriginal and Torres Strait Islander population [4].

Vaccinations, along with appropriate sanitation and hygiene, are the primary public health interventions aimed at preventing rotavirus infections [6]. Rotavirus vaccination in Australia was introduced onto the NIP in 2007 and was followed by rapid uptake among vaccine-eligible children [10]. Two rotavirus oral live attenuated vaccines are available for use in Australia – Rotarix, a monovalent vaccine given on a 2-dose schedule, and RotaTeq, a pentavalent vaccine given on a 3-dose schedule [3, 7]. Prior to 2017, Victoria primarily offered RotaTeq, which was funded under the NIP. However, since 2017 all Australian states and territories offer Rotarix under the NIP, at 2 and 4 months of age [3, 12].

Rotavirus is classified into genotypes according to a binary system of the outer capsid proteins – G (glycoprotein) and P (protease-sensitive) genotypes [13-16]. A small number of genotypes contribute 80-90% of infections [15, 16], and currently the most prevalent genotypes in Australia are G1P[8], G2P[4], G3P[8], G9P[8] and G12P[8] [13, 16]. Rotarix, the most commonly used vaccine, targets a single human G1P[8] strain, whilst RotaTeq targets G1P[5], G2P[5], G3P[5], G4P[5], G9[5] [4]. Several new genotypes have emerged in recent years and there is some evidence that vaccine-induced selective pressure may be leading to changes in circulating genotypes in Australia [9, 14-16]. This highlights the importance of ongoing surveillance to inform the rotavirus vaccination program [16].

Rotavirus surveillance in Victoria

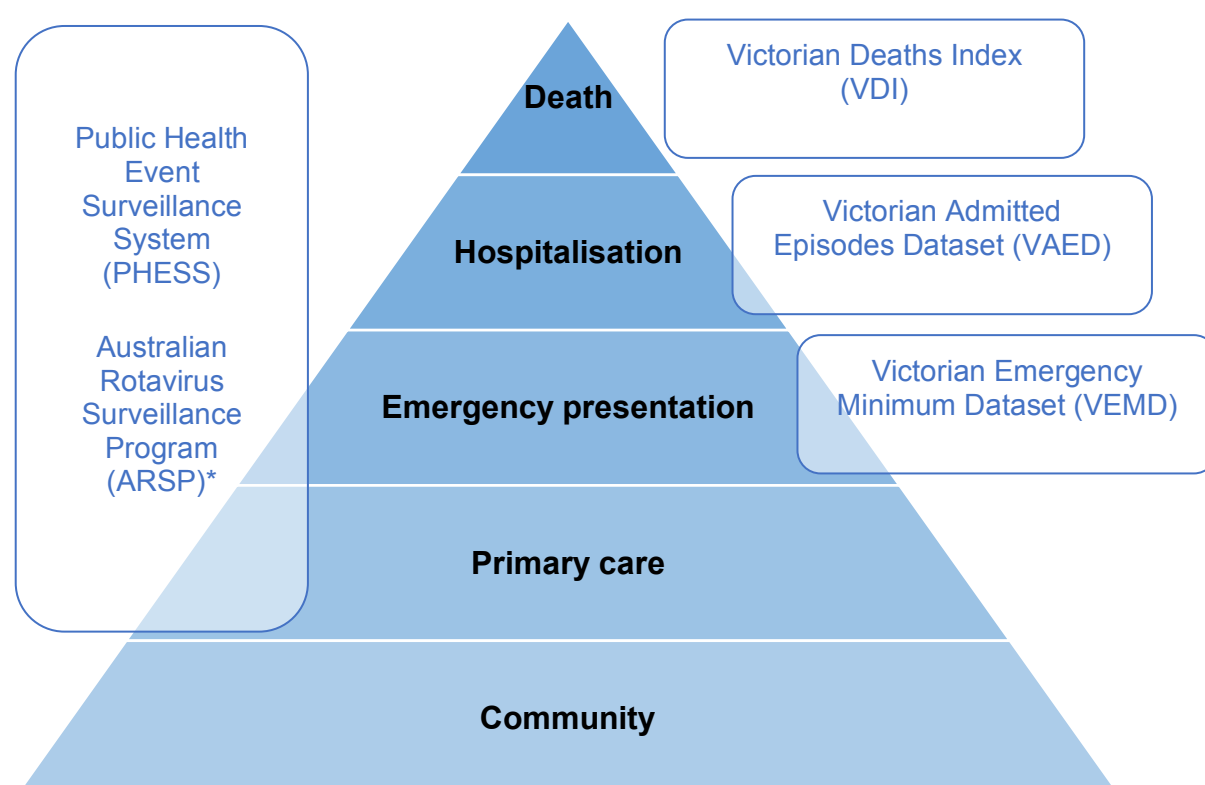
There are several surveillance systems in place that collect data on rotavirus case notifications, emergency presentations, hospitalisations and deaths in Victoria (Figure 1). In addition, data on rotavirus vaccinations is collected through the Australian Immunisation Register (AIR).

Rotavirus was added to the National Notifiable Diseases List in Australia in 2017 and became notifiable in Victoria in September 2018. Data on all rotavirus cases that meet the national notifiable diseases case definition [17] are recorded in Victoria's Public Health Event Surveillance System (PHESS). This includes cases who present and are tested at all levels of the healthcare system (Figure 1). Pathology services are required to notify the Department of Health (DH) within five days of detection of rotavirus in faecal samples, however medical practitioners are not required to notify cases of rotavirus [18]. Data on rotavirus outbreaks that occur within Victoria are also recorded in PHESS. There is currently no routine public health follow-up of rotavirus cases in Victoria other than management of occasional rotavirus outbreaks in childcare, schools or residential settings such as ACF.

Data on individuals who present to a public Emergency Department (ED) in Victoria are included in the Victorian Emergency Minimum Dataset (VEMD), and data on individuals who are admitted to a public or private hospital in Victoria are included in the Victorian Admitted Episodes Dataset (VAED). These datasets can be searched for rotavirus related presentations using the *International Statistical Classification of Diseases and Related Health Problems, tenth revision, Australian Modification* (ICD-10-AM) code A08.0 'Rotavirus enteritis'. Data on individuals who die in Victoria are reported to the Victorian Deaths Index (VDI) and this dataset can be searched using terms such as 'Rotavirus' to identify individuals who have died with the condition. Cases who present to an ED or hospital with rotavirus, or who die with rotavirus, should also be captured as case notifications in PHESS (Figure 1).

The Australian Rotavirus Surveillance Program (ARSP) is an additional national laboratory surveillance system that supports rotavirus surveillance within Victoria. The ARSP tests and subtypes a subset of rotavirus positive samples sent from participating laboratories across Australia, including from a selection of laboratories in Victoria. Genotyping of rotavirus strains plays an important role in surveillance, providing evidence to inform vaccination program introduction and implementation, including monitoring for vaccine effectiveness and vaccine-escape variants and the emergence of new genotypes [14, 16]. Characterising rotavirus genotypes can also support outbreak identification and management.

Figure 1: Surveillance systems capturing rotavirus epidemiological data in Victoria, 2023



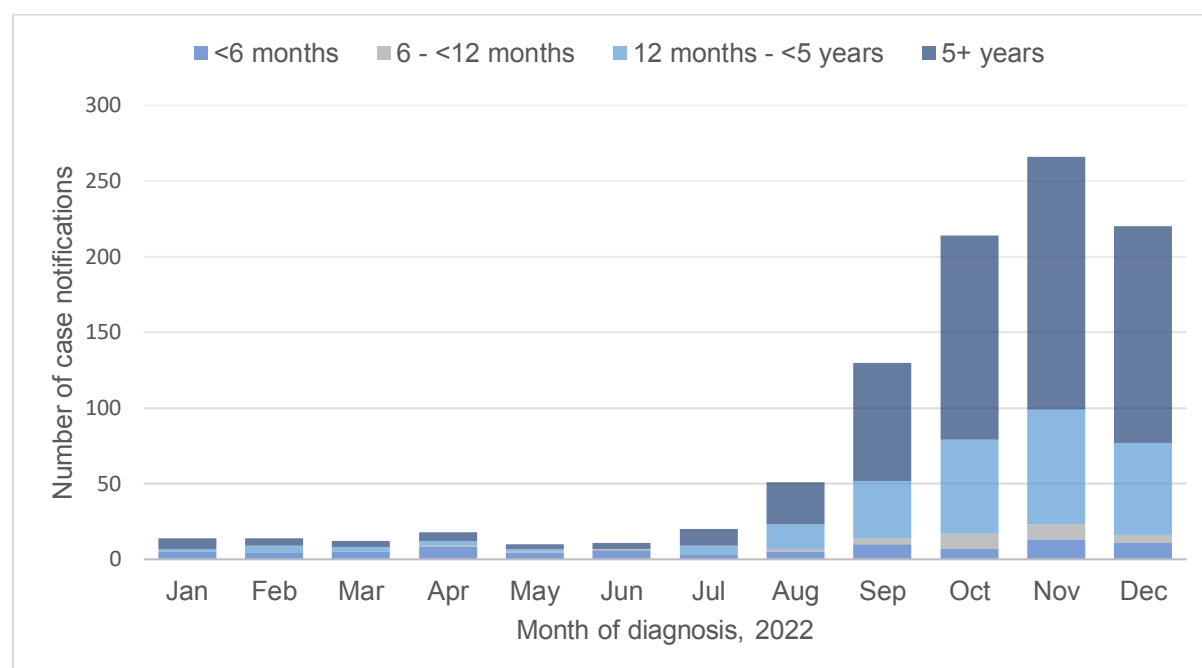
*A selection of laboratory confirmed rotavirus samples are sent to the ARSP for genotyping

Rationale for the evaluation

This evaluation was initiated by the Victorian Department of Health (DH) in collaboration with the director of the ARSP. DH and the ARSP had commenced earlier discussions regarding possibilities to enhance rotavirus surveillance in Victoria. In late 2022, Victorian notifiable disease surveillance data showed an increase in rotavirus notifications compared to previous years (Figure 2). There was insufficient evidence to understand the underlying causes of this trend, particularly as there was limited genotyping data available to DH. This reinforced the need to consider opportunities to enhance surveillance of rotavirus, to better understand

changes in the epidemiology of the disease in Victoria, and inform future changes to vaccination programs.

Figure 2: Rotavirus cases notified to Victoria's Public Health Event Surveillance System in Victoria by month of diagnosis and age group, 1 January to 31 December 2022



Genotyping of rotavirus samples can provide valuable information to support Victorian rotavirus surveillance. The ARSP was previously evaluated at a national level in 2008 [19], but since Victoria switched from using RotaTeq to Rotarix in 2017, and rotavirus became a notifiable disease in the jurisdiction in 2018, an evaluation of the system has not yet been undertaken focussing on the Victorian context.

Evaluation objectives

This evaluation focused on the Victorian component of the ARSP and did not consider the broader national program. A full and thorough evaluation was undertaken to understand the strengths, weaknesses and attributes of the current system in the Victorian context. The key objectives of the evaluation were to:

- identify the strengths of the ARSP in Victoria, and any opportunities for potential improvements;
- understand whether the subset of samples included in the ARSP is representative of rotavirus cases in Victoria; and

- consider whether there is scope to expand the ARSP in Victoria by increasing the number of samples or the number of laboratories providing samples to the ARSP.

This evaluation sought to identify opportunities to enhance the current program to better support Victoria's broader rotavirus surveillance system.

METHODS

Framework

The Centers for Disease Control and Prevention (CDC) Updated Guidelines for Evaluating Public Health Surveillance Systems (CDC Guidelines) were used as a framework for the evaluation [1]. The CDC Guidelines outline nine attributes of a surveillance system. Each attribute was considered in the evaluation (Table 1), with some attributes such as representativeness receiving greater focus based on the initial objectives of the evaluation and feedback from respondents. The aspects of the attributes investigated were refined through key informant interviews with DH and MCRI respondents.

Table 1: Attributes of the CDC Guideline evaluated, aspects investigated and methods of assessment

Attribute	Aspects investigated	Method of assessment
Simplicity Structure and ease of operation	• How much data, and what type of data are collected? • How simple is collecting and analysing the data? • How simple is reporting and interpreting the data? • How well integrated is the ARSP with other systems? • How much time and resources are required to operate the system?	• Documentation review • Key informant interviews
Stability The reliability and availability of the system	• What resources are required to operate the system and are these met under current arrangements? • How regularly is the ARSP operating? • Are laboratories consistently providing samples to the ARSP? • What is the coverage of collaborating laboratories compared to laboratories conducting rotavirus testing in Victoria?	• Documentation review • Key informant interviews • ARSP and DH data
Acceptability	• Is MCRI willing to continue operating the ARSP?	• Key informant interviews

Willingness to participate in the surveillance system	• How many laboratories are collaborating and are these willing to participate? • How many laboratories are not collaborating and what are the barriers to participating? • How is DH willing to support the ARSP?	
Timeliness The time taken between each step in the surveillance system	• How long does it take from initial test positivity, to receipt of sample at MCRI, to processing results and reporting results? • How regularly does ARSP report results to DH? • How long do <i>ad hoc</i> requests for data take to process?	• Documentation review • Key informant interviews
Flexibility How the system adapts to changing informational needs or operating conditions	• How flexible has the system been to past changes? • How flexible would the system be to expanding its current scope? • Would the system be able to cope with increasing the number of samples analysed / collaborating laboratories? • Is the system able to cope with <i>ad hoc</i> requests for analysis and reporting (e.g. during outbreaks)?	• Documentation review • Key informant interviews
Data quality Data completeness and validity of the data recorded	• How many samples received are able to be analysed? • How complete is the submission form (epidemiological data) accompanying samples? • How complete is the final reported data?	• Documentation review • ARSP data • Key informant interviews
Positive predictive value Proportion of reported illness that have the condition under surveillance	• What proportion of samples are confirmed to be rotavirus-positive?	• ARSP data
Sensitivity Ability to detect outbreaks and monitor changes in the number of cases over time	• What proportion of rotavirus tests are sent to the ARSP for typing? • Has the ARSP ever detected an outbreak that DH was not previously aware of? • How many outbreaks has the ARSP supported investigating?	• Documentation review • ARSP and DH data • Key informant interviews
Representativeness Accurately describes the characteristics of rotavirus in the Victorian context	• How well does the subset analysed by the ARSP represent the population of rotavirus cases reported in Victoria?	• ARSP and DH data

Documentation review

Information to support describing the ARSP, understanding its usefulness, and assessment of some attributes (Table 1) were sourced from the ARSP annual reports [20] and internal documentation from the ARSP and DH that was provided by respondents.

Consultation

Relevant stakeholders were identified by DH, MCRI and through the documentation review. There were four main groups identified:

- MCRI: staff members who currently or have formerly operated the ARSP, and the Surveillance of Adverse Events following Vaccination (SAEFVIC) unit;
- DH: epidemiologists and staff who work within the communicable diseases unit and the immunisation unit;
- Collaborating laboratories: Victorian diagnostic public and private laboratories which currently or had previously contributed to the ARSP; and
- Non-collaborating laboratories: Victorian diagnostic public and private laboratories which undertake rotavirus testing within Victoria but do not currently contribute to the ARSP.

From September 2018 to December 2022, 10 Victorian laboratories had reported rotavirus cases to DH. Some had only reported a very small number of cases. To ensure the evaluation sought input from relevant respondents, only laboratories that had notified at least 30 cases over the three years (average 10 per year) were invited to participate in the stakeholder consultations.

Questionnaires were designed for each of the four main respondent groups. Respondents were identified via MCRI or using internal DH contact information (i.e. the designated laboratory contact for each laboratory – typically the head of the laboratory). Respondents were sent an email with an information sheet and invited to participate in a 30 minute video interview. Respondents were offered the option of providing written feedback if they were unable to participate in a video interview. In total, 11 of the 15 (73%) respondents who were invited agreed to participate. The majority (n=10) participated in a video interview, with one providing written responses to their relevant questionnaire (Table 2). Two contact attempts were made for respondents who did not participate. For those that did not respond to requests for interviews, this may have been due to a variety of reasons including lack of interest and competing priorities. Only one laboratory provided a reason for not participating (key personnel were on leave and there were competing priorities). Respondents were invited to

bring additional team members to the interview if they wished. Video interviews were conducted over Microsoft Teams and were recorded and transcribed by the platform, with transcriptions verified by reviewing recordings. Respondents provided additional information through follow-up emails where required.

Interviews were semi-structured utilising developed questionnaires as a basis, with additional questions asked based on responses received (sample of questions provided at Appendix A). The developed questionnaires were internally piloted and refined based on feedback to improve face validity and internal consistency. Results are presented as a proportion if respondents were answering a standardised question, or as a raw number of respondents who raised a theme in response to any question during the interview.

Table 2: Respondents engaged to participate in the evaluation through key informant interviews or written responses

Respondent group	Number invited	Number participated	Attributes assessed
Murdoch Children's Research Institute • Current and former ARSP program directors • Surveillance of Adverse Events following Vaccination (SAEFVIC)	3	2*	Simplicity, Stability, Acceptability, Flexibility, Timeliness, Data quality, Sensitivity, Representativeness
DH Staff • Communicable Diseases Epidemiology and Surveillance unit • Immunisation unit	3	3	Simplicity, Stability, Acceptability, Flexibility, Timeliness, Sensitivity, Representativeness
Staff from laboratories which currently participate in the ARSP	3	3*	Simplicity, Stability, Acceptability, Flexibility, Timeliness, Data quality, Sensitivity, Representativeness
Staff from laboratories which formerly participated in the ARSP	1	0	Simplicity, Stability, Acceptability, Flexibility, Timeliness, Representativeness
Staff from laboratories which have never participated in the ARSP	5	3	Simplicity, Stability, Acceptability, Flexibility, Timeliness, Representativeness

* In some interviews and written responses, several representatives from an organisation participated. The number presented here represents the total organisations/teams invited to participate, and more individuals participated within these categories.

Data analysis

De-identified aggregate level data on Victorian samples analysed through the ARSP were sourced from the MCRI. Data were extracted from 2012 to 2022, to provide a long-term view of the program. De-identified line listed data on Victorian rotavirus notifications (i.e. those with a positive laboratory result) were sourced from PHESS and included cases residing in Victoria and cases who have an interstate residential address that were notified by a Victorian laboratory. Data were extracted from September 2018 to December 2022, as rotavirus only became notifiable in Victoria in September 2018.

Results were limited to samples sent from Victorian laboratories for both the ARSP and PHESS datasets. Therefore, Victorian residents who received rotavirus testing interstate or overseas were excluded from the analysis. Individuals with a residential address outside of Victoria (interstate or overseas) were included if they had a rotavirus sample tested at a Victorian laboratory that was either sent to the ARSP or notified and recorded in PHESS.

Data analyses were undertaken using Stata v.16 [21] and Microsoft Excel (2022). Maps were produced in R version 4.1.2 [22]. For the ARSP dataset, locality data (postcodes) were mapped to Local Government Area (LGA) using Victoria's 2021 postcode locality reference [23]. All datasets were descriptively analysed to identify changes over time and produce summary statistics and figures.

Ethics

Ethics approval has been provided by the Australian National University Human Research Ethics Committee under protocol 2017/909. Oral consent was obtained at the start of respondent interviews, as is standard in public health practice.

RESULTS

Description of the ARSP

Structure and governance

The ARSP runs through the National Rotavirus Reference Centre (NRRC), which is the World Health Organization (WHO) Rotavirus Regional Reference Laboratory for the Western-Pacific Region, operated by the MCRI at the Royal Children's Hospital (RCH), Melbourne, Australia. It is the only surveillance system in Australia to focus on rotavirus genotyping and has been running in its current form since 1999. The ARSP operates within MCRI's governance structure and utilises the same general systems (e.g. laboratory, IT systems). The program has been reviewed by the RCH Human Research Ethics Committee and was deemed a

Quality Activity and Evaluation project that adheres to relevant ethical principles of State, Territory and Commonwealth legislation. Consequently, there are no ongoing legislative or ethical approvals required to operate the program. The ARSP only receives de-identified laboratory information on a voluntary basis, and results do not directly influence patient care.

The ARSP is a national laboratory surveillance system, with both public and private laboratories around Australia able to become 'collaborating laboratories' regularly providing rotavirus positive samples to the ARSP for genotyping. These collaborating laboratories are not static, with laboratories from six or seven (out of eight) Australian states and territories contributing to the ARSP in recent years. Collaborating laboratories are not directly involved in the program and receive no funding, incentives or direct support to participate.

Resourcing

The ARSP is supported by grants from the Australian Government Department of Health and Aged Care (DOHAC) and GlaxoSmithKline Biologicals SA (GSK). CSL Seqirus previously supported the ARSP, however funding ceased in 2017 when all states and territories transitioned to Rotarix on the NIP. Funding is re-negotiated periodically, with the DOHAC agreement currently in place for 3 years with an option for a contract extension and the GSK agreement re-negotiated periodically as required (between 1 and 3 years based on funder preference). Funding is received on approval of the annual report and/or at agreed time points. Funding for the program has varied based on the activity projected and is provided for analysis of a minimum number of samples (currently 750 nationally representative samples). In some years, the number of samples has exceeded the funds available and in other years this threshold has not been reached (for example, during the COVID-19 pandemic years 2020–2021).

Funding is provided to cover basic laboratory equipment, laboratory consumables, and packaging and courier of samples from all laboratories across Australia including Victoria to the ARSP. There is no funding available to reimburse collaborating laboratories for the time required to coordinate and package samples for the ARSP. Funding for the ARSP covers 1.3 full time equivalent (FTE) laboratory-based staff. However, these human resources are supplemented from the broader MCRI budget. All staff in the NRRC laboratory are involved in rotavirus surveillance, even if they are not directly part of the ARSP. Personnel cover all areas of expertise currently required to operate the program.

Objectives

The ARSP was initially established with the aim of monitoring the epidemiology of rotavirus and better understanding severe disease due to rotavirus in children, and later was used to inform the implementation of a rotavirus vaccination program (after rotavirus vaccines RotaTeq & Rotarix became registered in 2006) and which vaccines were used on the NIP (from 2007). The initial objectives of the ARSP were documented in a 2008 evaluation of the system [19]. Respondents who have been involved with the program long-term considered that the ARSP was highly effective at meeting its initial objectives (n=2). However, there have been considerable changes in rotavirus vaccination programs and epidemiology in recent years, with rotavirus vaccines becoming available on the NIP, the transition from RotaTeq to Rotarix, and the ARSP expanding its focus to include adults as well as children. As part of this evaluation, the ARSP considered and updated the program objectives to:

- undertake surveillance and characterisation of rotavirus strains causing gastroenteritis in Australian states and territories;
- characterise and report on rotavirus genotypes causing outbreaks to assist in the public health response to the outbreak;
- compare data on rotavirus epidemiology prior to and after the introduction of rotavirus vaccines and in response to changes in the specific vaccine or schedules, in order to document if patterns in rotavirus genotypes change in response to vaccine pressure;
- add to knowledge of rotavirus epidemiology in Australia and in a global context which, in turn, contributes to vaccine development; and
- develop expertise in rotavirus genotyping and sequencing and surveillance which can be shared nationally and globally.

Recommendation: The ARSP to regularly review and document objectives for the program, in collaboration with their funders (at least every 5 years and when major changes in rotavirus surveillance occur). This will inform future priorities for the program and ensure objectives of the system are meeting the changing requirements of rotavirus surveillance.

Processes

A flow chart of the processes to operate the ARSP in Victoria is outlined at Figure 3.

For routine rotavirus cases (sporadic community and hospitalised cases), diagnostic testing is first conducted by a collaborating laboratory before a specimen is sent to the ARSP. As a standard process in the management of viral gastroenteritis outbreaks in Victoria, all samples must be sent to the Victorian Infectious Diseases Reference Laboratory (VIDRL), either directly or via the Microbiological Diagnostic Unit (MDU) Public Health Laboratory. Samples are then sent from VIDRL to the ARSP, however the specific processes are not currently formalised.

Initial diagnostic testing is conducted by reverse transcription polymerase chain reaction (RT-qPCR), enzyme immunoassay (EIA), or latex agglutination. Positive samples are stored frozen between -20°C and -70°C at the collaborating laboratory until sent to the ARSP for genotyping. For routine samples, the ARSP sends requests for samples at predetermined intervals, typically four to six times per year. For samples of public health significance including outbreaks, these can be sent as a priority outside of aforementioned timeframes. Collaborating laboratories complete an Excel form with associated metadata for each sample. Requested data fields include date of collection, date of birth, sex, postcode of residence, hospitalisation status, Indigenous status, and vaccination status (whether or not vaccinated – vaccine type is assumed to be Rotarix and the date of vaccination is not typically provided unless vaccine identification for a patient has been requested). Collaborating laboratories batch all positive samples for transport, and either the ARSP arranges a courier to collect them or the collaborating laboratories use their own courier, if they choose.

Once at the NRRC, samples are stored at -80°C until analysed. The specific testing algorithm and process used is documented in annual reports and has evolved over time [20]. The current process is briefly summarised here. Samples that are duplicates, missing samples (i.e. listed in documentation but not physically present) or insufficient samples are excluded from the analysis; for duplicate samples, the first sample is typically tested unless the first sample volume is inadequate or gives inconclusive results. A hemi-nested multiplex RT-PCR assay is used to determine rotavirus G- and P- genotypes. The first round of genotyping involves the One Step RT-PCR kit (QIAGEN) in conjunction with VP7 (VP7F/VP7R) or VP4(VP4F/VP4R) conserved primers. The second round of genotyping involves PCR reactions using specific oligonucleotide primers for G types G1, G2, G3, G4, G8 and G9 or P types P[4], P[6], P[8], P[9], P[10], and P[11]. If the sample does not generate a second round PCR amplicon or has inconclusive results, further testing is conducted using VP6-specific RT-PCR. Sanger sequencing is used to determine the VP7 and/or VP4 nucleotide sequence for PCR non-typeable or VP6 positive samples. The VP7 gene of each G1P[8] sample is sequenced to determine whether the sample is a wildtype or Rotarix vaccine strain.

Data analysis and management

All information received by the ARSP is de-identified. MCRI has a standard operating procedure for managing samples with identifiable data, if it is received in error. In summary, a staff member from the RCH microbiology diagnostics laboratory is employed to manage samples with identifiable data so that ARSP staff do not handle samples until identifiable data is removed. Any physical identifiable information is securely shredded and emails with identifiable information are deleted. Individuals who have mistakenly provided identifiable data are contacted to reinforce the need to de-identify information before sending it to the ARSP.

Once samples arrive at MCRI, they are allocated a unique laboratory code and entered into the NRRC database (Excel and REDCap) along with associated metadata. All laboratory results are kept in the NRRC database. Only approved personnel who have been directly given access to REDCap by the database administrator are able to access the project database. There are varying levels of access that can be granted depending on the role of the individual staff member. The database is password protected and requires two-factor authentication for login. Data analyses are typically done using Microsoft Excel or Stata.

Reporting

The primary output of the ARSP are the annual reports which are provided to the program funding partners (DOHAC and GSK) and are made publicly available through the *Communicable Diseases Intelligence* journal [20]. These annual reports provide detailed aggregated results of the national program.

Additional individual-level laboratory results are provided to collaborating laboratories. In the past, collaborating laboratories received all individual results, however collaborating laboratories (2/3) advised this is no longer occurring. An MCRI respondent advised that routine sharing of information stopped due to limits in the capacity of the program but could be reinstated in the future if requested by stakeholders. Individual results are still provided to groups who have requested this information. Currently, only one collaborating laboratory (1/3) is receiving all individual sample results as most of their cases are related to outbreaks. The remaining collaborating laboratories (2/3) reported only receiving results for cases that they have requested information on, or were of public health significance such as outbreak cases or where vaccine excretion is suspected.

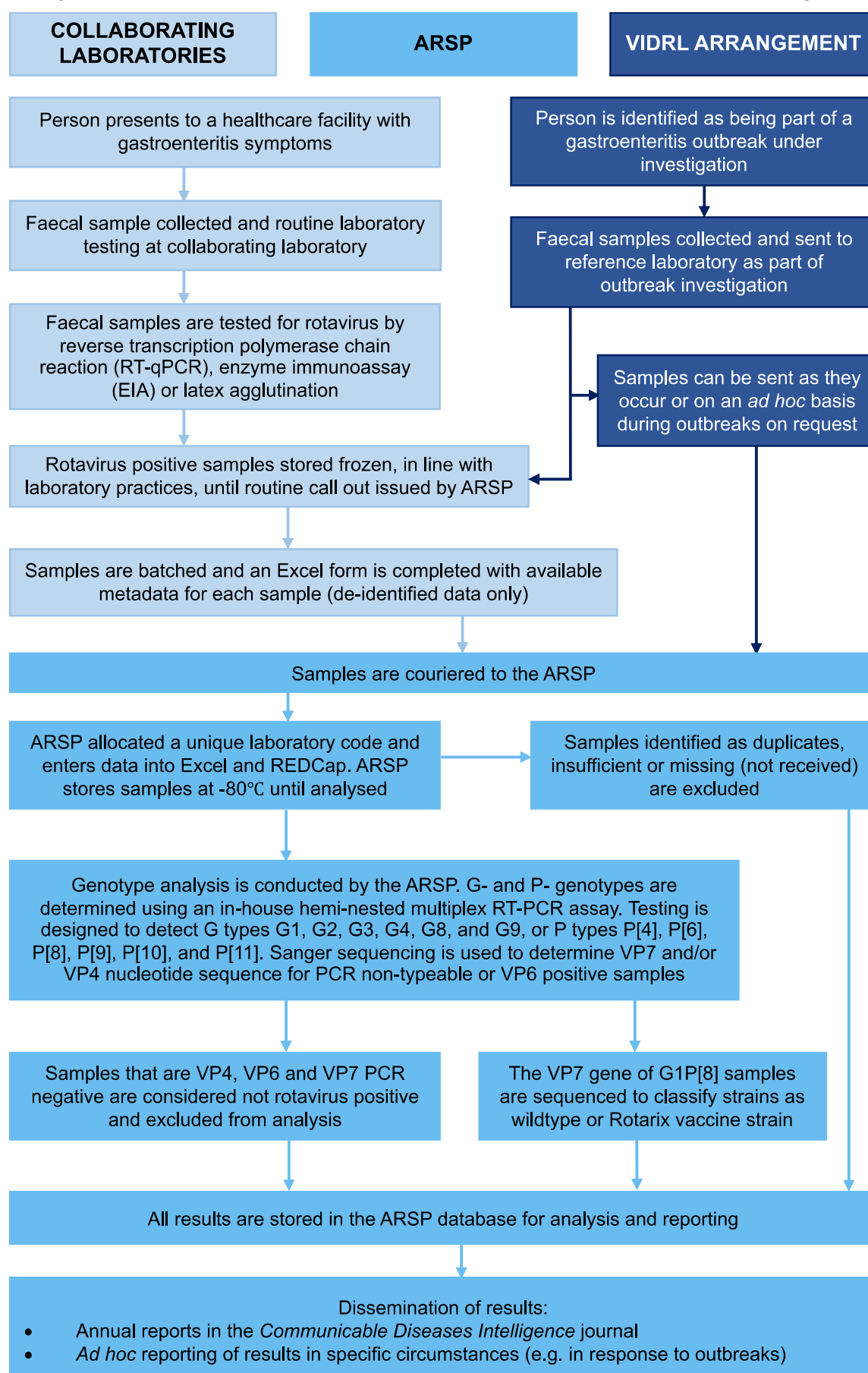
The ARSP has the capacity to provide line-listed data of results to jurisdictional health agencies such as DH. However, sharing of raw data requires a material transfer agreement², and currently the ARSP does not have an agreement in place with DH.

Recommendation: DH and the ARSP should work together to develop a material transfer agreement to support the sharing of line-listed data.

Strength: Respondents noted that the historical standing of the program was relatively unique to Australia. The program has published over 20 years of annual reports, providing a strong evidence base to inform policy and research.

² A material transfer agreement is a legal agreement that allows the transfer of research materials between two organisations and defines how the information can be used.

Figure 3: Flow chart of processes in the Australian Rotavirus Surveillance Program



Assessment of attributes

Simplicity

Amount and type of data collected

Between 2012 and 2022, the ARSP received a mean of 128 samples annually from Victorian laboratories (range 52 to 205). The requirements for the collection, storage and sending of laboratory samples has remained unchanged, with samples already being collected for diagnostic purposes. The metadata requirements have increased over time, with data fields for hospitalisation status added in 2016, Indigenous status added in 2020, and vaccination status added in 2022.

All respondents from MCRI (2/2) and collaborating laboratories (3/3) agreed that the data requirements were simple, with well-established processes operating over many years. Some respondents from both collaborating and non-collaborating laboratories (3/6) noted that completing the metadata form could be challenging, as some new data fields such as vaccination status are only available in patient records and not on pathology request forms.

Respondents from MCRI (n=1) and collaborating laboratories (n=2) also noted that collecting data in relation to outbreak samples was a complicating factor, as there was “*competition*” for samples between MCRI and VIDRL. Respondents from MCRI (n=1), DH (n=1) collaborating laboratories (n=1) and non-collaborating laboratories (n=1) agreed there was a need for an established and formalised pathway where all outbreak samples would first go to VIDRL and then be forwarded to the ARSP for additional testing.

Time and resources required to operate the ARSP

Respondents from MCRI (n=1) and collaborating laboratories (3/3) agreed that the system was straightforward, describing the time and resourcing requirements as “*not onerous*” and “*fairly simple and cost-effective*”. The ARSP intentionally staggers call outs for routine samples throughout the year to ensure their laboratory capacity is not overwhelmed and there is diversity in samples across seasons. The ARSP occasionally faces increased workloads when following up collaborating laboratories to collect samples or when supporting an outbreak investigation (either locally or interstate) which can increase the time required to support the program.

Collaborating laboratories (3/3) identified challenges in collecting and compiling metadata due to time requirements, with one noting “*it’s not difficult, it’s more time consuming than anything*”

e/se". Laboratories suggested that this process could be made simpler by having clear instructions on the minimum data requirements for samples (n=1) or being permitted to supply the ARSP with extracted data from their existing computer systems, rather than separately completing the ARSP's metadata Excel form (n=1).

Strength: The ARSP processes are easy to follow. The program is seen as simple and cost-effective.

Analysis, reporting and interpreting the data

The ARSP has published annual reports in the *Communicable Diseases Intelligence* journal every year since 1999 [20]. MCRI noted that preparing the annual report was time consuming, however the analysis was straightforward and could readily be done using Microsoft Excel and Stata. Respondents did not express any concerns about the ARSP's capacity or capability to meet their current reporting requirements.

Some respondents from collaborating laboratories (2/3) expressed difficulty in understanding and interpreting the results when provided individually to collaborating laboratories and/or in the annual report. These respondents noted that it was helpful when the ARSP provided additional context about what new strains meant from a population health perspective. Collaborating laboratories (3/3) expressed a strong desire to receive line-listed individual results from samples they contribute to the system with some basic interpretation of what the results mean.

Integration with other systems

The ARSP is not integrated into other rotavirus surveillance systems in Victoria. In particular, respondents from DH (2/3) noted that there was limited utility to the data as it could not be linked back to case data in PHESS, stating that "*it's just too separate from our other epidemiological data*". An MCRI respondent noted that there were systems in place in other jurisdictions, such as Western Australia, to enable linkage to their routine surveillance systems. Respondents from DH (2/3) and MCRI (n=1) agreed that integrating the ARSP data into PHESS would simplify rotavirus surveillance systems in Victoria and provide additional richness to the available data.

Area for improvement: The ARSP is not integrated with other rotavirus surveillance systems in Victoria, particularly PHESS. This makes it harder to understand the results in the Victorian context and limits the utility of the data.

Recommendations:

- DH and the ARSP work together to identify a pathway to integrate genotyping data into PHESS. This could be achieved by the ARSP providing line listed data with laboratory ID directly to DH, or by the ARSP routinely reporting results to collaborating laboratories, who can then provide updated results to DH.
- DH liaise with VIDRL and formalise arrangements for all outbreak samples to be sent to the ARSP for genotyping, following VIDRL testing. The DH outbreak identifier should be sent with all samples to allow results to be linked back to PHESS as outlined above.
- The ARSP assess the feasibility of receiving metadata in other formats such as data extracts from laboratory systems or setting up a database in a system such as REDCap that the laboratories can use to transmit data. If there are no ethical or governance barriers to this approach, this should be accepted to minimise the time commitment required from collaborating laboratories.
- The ARSP review current documentation for collaborating laboratories to ensure clear instructions on minimum data are incorporated.

Stability

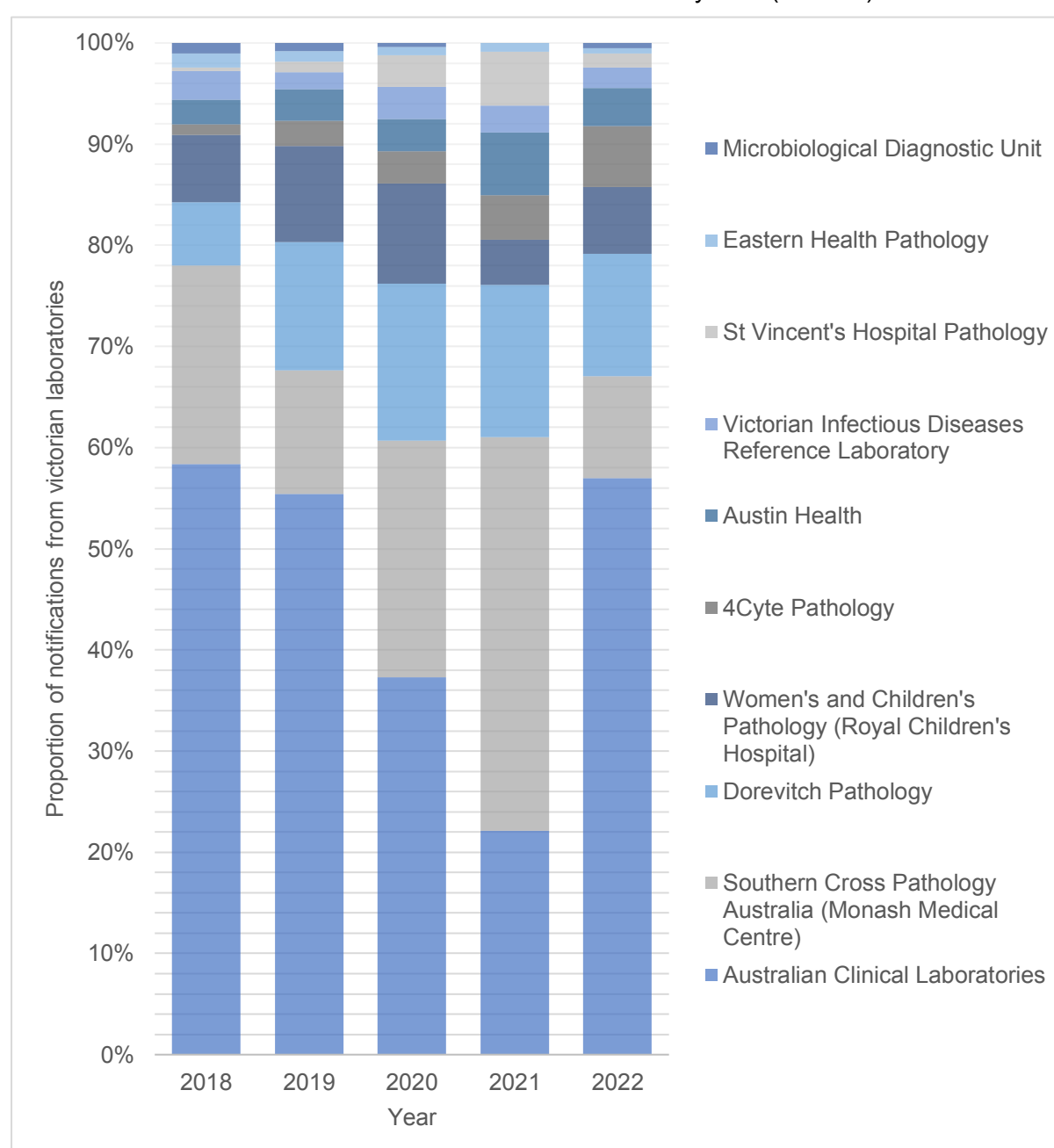
System resourcing

Some respondents from MCRI (2/2) and a collaborating laboratory (1/3) noted that resourcing was unstable due to a reliance on two external funders and the need to re-negotiate on a regular basis, with one respondent highlighting that the program had historically been “*operating on a shoestring budget*”. However, MCRI advised that funding was currently adequate to cover the operating costs of the program, noting there are limitations to how funding can be utilised and it cannot be directly provided to collaborating laboratories, restricting the ability to expand the program and potentially to meet future rotavirus surveillance needs.

Engaging and retaining collaborating laboratories

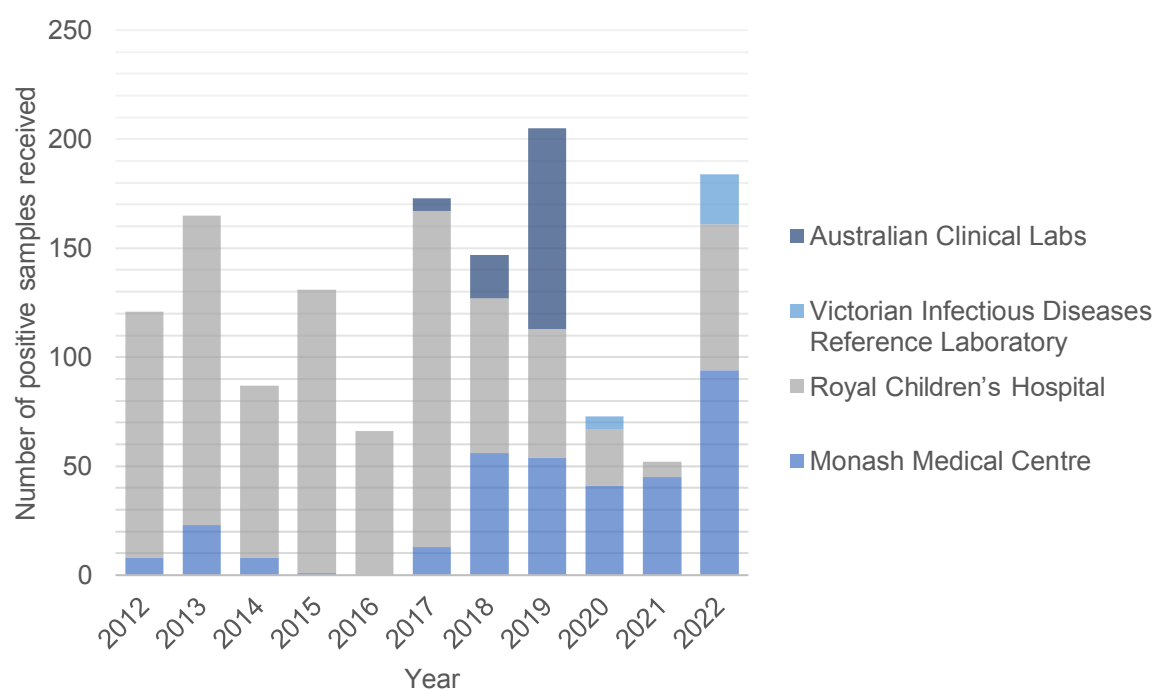
Most respondents from MCRI (2/2), DH (1/2) and collaborating laboratories (2/3) agreed that engaging and retaining collaborating laboratories was a significant challenge and was the greatest threat to the stability of the ARSP. Ten laboratories currently undertake rotavirus testing in Victoria, with the greatest proportion of positive samples in recent years being tested by Australian Clinical Laboratories (ACL), Southern Cross Pathology at Monash Medical Centre (MMC) and Dorevitch Pathology (Figure 4).

Figure 4: Proportion of rotavirus notifications from Victorian laboratories, 2018 to 2022 as recorded in the Victorian Public Health Event Surveillance System (PHESS)



Between 2012 and 2021, four collaborating laboratories in Victoria contributed to the ARSP, with RCH and MMC contributing throughout this time, ACL contributing from 2017 to 2019, and VIDRL contributing in 2020 and 2022 (Figure 5). A large proportion of Victorian samples are currently not being captured by the ARSP, with none of the major private laboratories currently collaborating (e.g. ACL, Dorevitch Pathology, 4Cyte Pathology). ACL has not contributed to the ARSP in recent years, despite PHESS data showing it notified more than half of positive rotavirus cases in 2022. As ACL did not respond to requests to participate in the evaluation, the reasons for their withdrawal from ARSP could not be explored in this evaluation.

Figure 5: Number of positive samples received by the Australian Rotavirus Surveillance Program (ARSP) by Victorian collaborating laboratories, 2012 to 2022



Respondents agreed that laboratory retention and ensuring laboratories consistently provide samples was a challenge for the ARSP. Most respondents from MCRI (2/2) and collaborating laboratories (2/3) agreed that further work was required to support retention, with some highlighting historical actions that have supported retention (Box 1). Some of these respondents (n=2) indicated that these historical actions had been successful but believed that since these actions were no longer implemented there is now a greater disconnect between the ARSP and collaborating laboratories, as currently there are fewer opportunities for engagement. Respondents from collaborating laboratories noted the greatest barriers to their continued participation in ARSP was the time taken to contribute to the program (3/3),

particularly completing the metadata requirements, and a lack of incentives or reimbursement (2/3).

Some respondents from MCRI (n=1), DH (n=1) and collaborating laboratories (n=1) also emphasised the impact of the COVID-19 pandemic on the stability of the ARSP particularly with regards to retention of laboratories, with one respondent noting “*COVID stuffed up everything. Labs didn’t have time to focus on rotavirus*”. Collaborating laboratories (2/3) expressed difficulty in finding time to contribute to the ARSP in recent years due to shifting priorities during the COVID-19 pandemic.

Box 1: Actions previously taken by the Australian Rotavirus Surveillance Program (ARSP) to support engagement and retention of laboratories

- Invitation and funding for all collaborating laboratories to attend an annual general meeting
- Staff from the ARSP travelling in person to laboratories to meet with staff and build relationships
- Providing small Christmas presents such as movie vouchers to staff
- Regular communications through newsletters, emails and phone calls

Most respondents from MCRI (2/2) and collaborating and non-collaborating laboratories (3/6) agreed that it was important to engage new collaborating laboratories in the ARSP, as this would build greater stability into the program, supporting existing collaborators who may need to stop contributing in the future. Of the laboratories who were not currently collaborating, none (3/3) were aware they could be contributing to the ARSP and none recalled being approached in the past to participate. All of these laboratories expressed interest in participating in the ARSP, with respondents across all groups (n=4) suggesting that DH may have a role in promoting awareness of the program and encouraging laboratories to be involved.

Areas for improvement:

- The ARSP is reliant on collaborating laboratories to operate, however it is challenging to attract and retain collaborators, with ACL, a major laboratory for rotavirus, no longer contributing to the ARSP.
- The ARSP funding model prevents collaborating laboratories from being provided with reimbursement or financial incentive to participate.

Ability to support outbreak responses

There were mixed opinions as to whether supporting outbreaks was a critical function of the ARSP, with one respondent from DH noting that “[*genotyping*] doesn’t change the public health response”. If this function continues, there is a need to simplify and formalise processes for outbreak investigations in Victoria, with samples to be initially sent to VIDRL prior to being sent to MCRI. Respondents from MCRI (n=1), DH (n=2) and collaborating laboratories (n=2) agreed that this would be the most consistent approach to ensuring the majority of laboratory samples are sent to the ARSP. Some respondents (n=3) noted that this process can pose challenges for the ARSP, for example resulting in an inadequate sample being available for genotyping analysis. Some respondents from DH (n=2) and collaborating laboratories (2/3) also noted that it was generally challenging to get rotavirus samples during outbreaks and that there was a need for DH to consider the recommended number of samples to collect during an outbreak and options to improve sample collection.

Recommendations:

- The ARSP explore with current funders the ability to initiate longer term funding terms or seek additional funding from other providers to improve the security and stability of the program.
- The ARSP seek additional funding to provide a nominal amount of financial reimbursement to collaborating laboratories.
- The ARSP invest in engaging new collaborating laboratories in Victoria and build upon relationships with existing collaborating laboratories, by providing more regular updates on the ARSP and opportunities to be more involved.
- The ARSP prioritise re-engaging Australian Clinical Labs (ACL) in the program.
- DH offer support to the ARSP to engage new collaborating laboratories, by providing the ARSP with information on laboratories conducting rotavirus testing in Victoria, and the appropriate contacts from these laboratories.
- DH facilitate the ARSP to present on the program at an appropriate forum such as a laboratory liaison meeting (a regular meeting convened by DH with Victorian laboratories) to build awareness of the program and demonstrate DH's support.
- DH facilitate introductions to laboratories where appropriate.
- DH update outbreak investigation protocols for rotavirus outbreaks, emphasising the importance of sample collection, detail the recommended minimum numbers of samples needed for an outbreak, and rapid transport to VIDRL.

Acceptability***Willingness to participate***

All respondents currently involved with the ARSP (4/4) were willing to continue working with the program. This included MCRI, who were willing to continue operating the ARSP into the future and were interested in expanding their role and responsibilities, and all collaborating laboratories. Five respondents, including DH (n=1), collaborating laboratories (n=1) and non-collaborating laboratories (3/3), were interested in increasing their involvement with the ARSP.

When asked why respondents were supportive of the program, laboratories noted a number of key reasons (Box 2), with respondents highlighting that the program is highly regarded internationally (n=3), and that respondents had trust and confidence in the way the program operates and the expertise of MCRI in conducting rotavirus laboratory surveillance (n=3).

Box 2: Reasons laboratories choose to participate in the Australian Rotavirus Surveillance Program (ARSP)

- Believing it is important to contribute to rotavirus surveillance and better understand rotavirus in Victoria (n=6)
- Getting information back on the genotypes of samples and having results validated (n=4)
- Having a long-standing history of contributing to the program (n=2)

Strength: The ARSP is well respected with a strong international reputation for excellence. Respondents have confidence and trust in the way the program is run and the accuracy of the data it produces.

There were mixed responses from DH regarding their willingness to be involved with the program, with one respondent wanting to be more actively involved in the program, but others (2/3) noting that they did not currently directly support the program and did not think it would be useful to increase their support.

Opportunities for improvement

Collaborating laboratories expressed some reservations (3/3), with general agreement from respondents (n=5) that more work was needed to improve the acceptability and conditions for collaborating laboratories into the future. Some laboratories (one collaborating and one non-collaborating) emphasised that the lack of funding or reimbursement was a barrier to their willingness to participate in the program. Respondents provided suggestions of non-financial incentives that could be offered to collaborating laboratories to overcome this limitation (Box 3), with respondents particularly highlighting the need for acknowledgment of contributors; “*everyone likes to be acknowledged and I must admit I don’t think they do that now*”. There was some tension noted between respondents due to perceptions that some collaborating laboratories received favourable treatment, with greater opportunities and acknowledgement. Despite this, all collaborating and non-collaborating laboratories (6/6),

including private laboratories (2/6) expressed a desire to collaborate even under the current conditions of the ARSP.

Box 3: Low-cost options to improve the willingness of laboratories to collaborate with the Australian Rotavirus Surveillance Program (ARSP)

- Ensure laboratories routinely receive the results of samples they contribute (i.e. whether positive or negative and what genotype)
- Increasing a sense of involvement in the program and products of the ARSP, such as increased involvement in reviewing annual reports and acknowledgments
- Formalising collaborating laboratories' relationships with the ARSP, for example through documentation and/or certificates of participation
- Offering collaborating laboratories opportunities to be involved in publications, particularly named authorship
- Building relationships through other research projects with MCRI (i.e. opportunities to be involved in publications that are not directly related to rotavirus or the ARSP)

Recommendations:

- The ARSP consider implementing low-cost options to improve the acceptability of the program for collaborating laboratories (see Box 3).
- The ARSP routinely provide results and outcomes of all rotavirus samples back to collaborating laboratories (whether positive or negative and genotype).
- The ARSP consider opportunities for both collaborating laboratories and other stakeholders such as DH to be involved in research outputs and publications, ensuring all collaborating laboratories have equal opportunities to be involved.
- The ARSP formally acknowledge all collaborating laboratories and personnel involved in the program in all research outputs.
- DH promote the ARSP to all laboratories undertaking rotavirus diagnostic testing at its internal discussions and relevant forums, including providing opportunities for the ARSP to present on the program.

Timeliness

Timeliness of analysis

According to respondents, once diagnostic laboratories receive rotavirus samples, initial testing typically takes between one and four days of receipt, depending on the laboratory receiving it and the circumstances of receipt (i.e. where the sample was collected, whether the sample is routine or outbreak). Routine samples are then stored for up to three months before batching and sending to the ARSP. MCRI (n=1) and collaborating laboratory (n=1) respondents noted that responsiveness to requests to send samples to the ARSP is variable, with some laboratories rapidly sending through samples and others requiring follow-up over a number of weeks or months. Collaborating laboratories (3/3) advised that for routine collections, it typically takes between four to 20 hours to coordinate and pack samples, and complete the associated metadata form to meet the ARSP requirements.

Data on the timing to process results was not available at the time of this evaluation. Respondents from MCRI (2/2) and collaborating laboratories (1/3) advised that once samples arrive at MCRI it can take between one and three months to analyse samples, depending on the volume received in the batch. One collaborating laboratory suggested that the ARSP reported back *“in a fairly timely fashion”*, as they had recently received results within one month. For samples prioritised for public health importance (including outbreak samples) results can be processed in between 48 hours and two weeks, depending on the complexity of the genotyping. Respondents from DH (n=1), MCRI (n=1) and laboratories (n=2) noted that timely collection of outbreak samples was typically a barrier to timely analysis and reporting of genotyping results. DH respondents (n=2) noted that the timeliness of reporting during outbreaks was critical, otherwise the data was of limited use.

Area for improvement: Results during outbreaks can take up to two weeks to process. This limits the utility of the information during an outbreak response.

Timeliness of reporting

Respondents from MCRI (n=2) noted that the ARSP does not have the ability to track rotavirus genotypes in real time as the primary output of the system is the annual report. Some respondents (3/11) felt that annual reporting was appropriate as long as other rotavirus data was made available in the interim, with some collaborating laboratories (2/3) noting line-listed data should be provided as results become available, even for community samples that are

not currently routinely reported to laboratories. Other respondents (2/11) wanted to see more frequent reporting, with one noting “*the whole concept of annual reports is a bit outmoded these days*”. MCRI respondents noted that *ad hoc* reporting could be provided more frequently during outbreaks, however they were not able to provide a local example as this has not occurred recently in Victoria.

Recommendations:

- The ARSP to commence collecting data on the date samples arrive and the date the sample is analysed to allow for the timeliness of the ARSP to be assessed in the future.
- The ARSP to provide outcomes of rotavirus samples back to collaborating laboratories (i.e. line-listed data) more frequently, for example quarterly once all analyses for a batch are complete.
- The ARSP to consider providing regular informal state-wide reporting to all partners within Victoria (e.g. quarterly or bi-annually). This could be done via email or a regular meeting, providing an overview of high-level trends being observed and to keep stakeholders engaged in the program.
- The ARSP continue to keep abreast of developments in new methodologies and technologies with the potential to speed up the processing of samples, particularly during an outbreak investigation.
- DH to update rotavirus outbreak management protocols to emphasise the importance in the timely collection of samples and sending to VIDRL for analysis. This should include recommended target timeframes.

Flexibility

Routine operations

MCRI respondents (2/2) noted that the ARSP has flexibly adapted to past system changes, highlighting the previous loss of CSL Seqirus as a major funder after the shift to the NIP only providing Rotarix. One MCRI respondent noted that frequently re-negotiating funding enabled the program to request additional funds when needed, however responses from funders could be mixed, with the deadline to supply annual reporting to funders being fairly inflexible.

The ARSP is able to add new data fields for metadata, and has added vaccination status, hospitalisation status and Indigenous status over the past decade. However, an MCRI respondent noted this could pose issues around ethics, as the current advice that no ongoing ethical approval is required may no longer apply. Additional data fields could also place an added burden on collaborating laboratories to locate and transcribe additional information in the required metadata form, which could also impact data quality due to incomplete data collection. Some collaborating (n=1) and non-collaborating laboratories (n=1) expressed a willingness to collect additional data as required, particularly if they could be involved in research outputs.

Responding to increases in rotavirus and outbreaks

Respondents from MCRI (2/2) and collaborating laboratories (n=1) noted there is a degree of flexibility built into the operations of the ARSP, allowing the program to accommodate fluctuations in rotavirus test numbers over time. MCRI respondents (2/2) noted the program “*can tolerate ups and downs*”, with a respondent highlighting that there were no significant changes to processes and timeframes during the recent increase in rotavirus cases in late 2022. Collaborating laboratories (2/3) noted that the ARSP was “*fairly flexible*” if they needed to send samples more regularly or if there were delays in sending samples.

MCRI advised that samples have not exceeded their maximum capacity in recent years, and they have had adequate funding and resources to analyse all samples. If there is an excess of samples, the ARSP would seek a representative sample by randomly selecting final samples for testing ensuring all jurisdictions are represented and including samples collected throughout the year. Respondents from MCRI and collaborating laboratories (3/5) noted that samples of public health importance could also be accommodated and prioritised by the ARSP throughout the year. An MCRI respondent indicated that the ARSP is able to produce *ad hoc* reporting to support rotavirus outbreaks.

Strength: The ARSP prioritises samples of public health importance associated with outbreaks throughout the year and can produce *ad hoc* reporting to support outbreaks if required.

Opportunities for expanding the ARSP

An MCRI respondent expressed a desire to increase the number of samples received and analysed, but noted they were limited by available funding. Collaborating laboratories (3/3)

advised that they are already routinely sending all positive rotavirus samples to the ARSP, and consequently the only avenue for increasing the number of samples from Victorian laboratories would be to engage new collaborating laboratories.

Existing collaborating laboratories (3/3) expressed that in-principle, they should be able to send rotavirus samples more frequently if required, with one noting they would need to consider if this would increase their time commitment to the program. Whilst all respondents from non-collaborating laboratories (3/3) were interested in contributing to the ARSP, some (2/3) noted a preference to send samples more frequently (i.e. monthly) instead of at the current routine call outs (i.e. four to six times annually) as they lacked space to store samples for longer than this.

Recommendations:

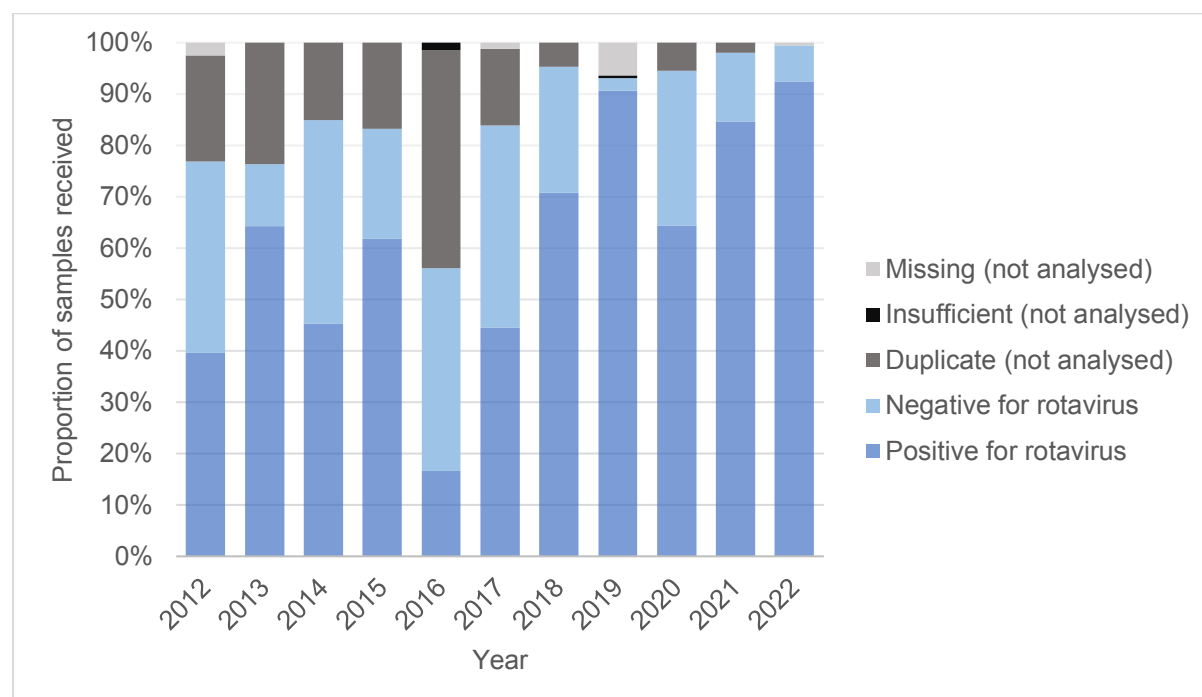
- The ARSP document the process for sample selection, in the event more samples are received than can be analysed in a year.
- The ARSP offer laboratories the option of sending samples at a higher frequency (i.e. monthly) to encourage new laboratories to collaborate.

Data quality

Laboratory data

From 2012 to 2022, a total of 1402 rotavirus samples were sent to the ARSP from Victorian collaborating laboratories. Of these, 1216 proceeded to analysis, and 186 were excluded from analysis as either duplicate samples (n=165, 12%), missing samples (n=19, 1%), or insufficient samples (n=2, 0%). Samples were defined as missing if they were listed on the spreadsheet provided by the collaborating laboratory but were not physically sent to the ARSP. The proportion of samples able to be analysed has increased over time, from 56% in 2016 (37/66) to 99% in 2022 (183/184) (Figure 6). All samples that proceeded to analysis were able to be genotyped. Respondents expressed confidence in the accuracy of the genotyping results.

Figure 6: Results from Australian Rotavirus Surveillance Program (ARSP) samples analysed and not analysed, 2012 to 2022



Strength: The ARSP has successfully genotyped all Victorian samples included in the analysis over the past decade.

Epidemiological data (metadata)

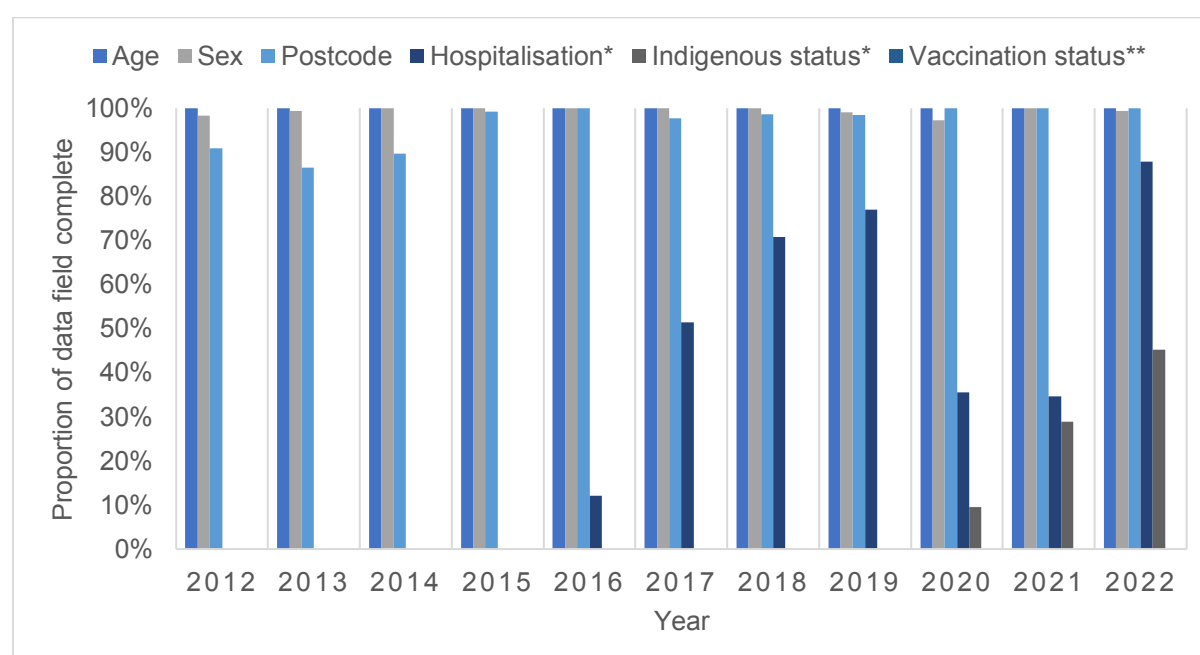
The completeness of epidemiological data varies between different data fields. Between 2012 and 2022, age was the most complete field (1399 of 1399, 100%), followed by sex (1391 of 1399, 99%), and postcode (1347 of 1399, 96%) (Figure 7). Each of these fields has been collected since the program's inception. An MCRI respondent noted that some fields, such as date of birth and date of collection, are essential for the analysis, whilst other fields, such as vaccination status, are not. The ARSP will routinely follow-up with laboratories to ensure essential data fields are complete.

New data fields that have been added in recent years generally had lower completeness (Figure 7). Since hospitalisation was added in 2016, 65% (561/861) of samples have had this information completed. Completeness of this data field initially increased between 2016 and 2019 before declining in 2020 and 2021 during the COVID-19 pandemic. Since Indigenous status was introduced in 2020, 49% (104/213) of samples have had this field completed. The

completion of the field has been gradually increasing. The newest data field, vaccination status (added in 2022), has not been completed in any of the Victorian samples (0/181, 0%).

An MCRI respondent noted that “*even once we start collecting data it doesn’t mean the lab will fill in the sheet*”. Respondents from collaborating laboratories (3/3) noted that they do not receive detailed information on vaccination status or Indigenous status, and to complete these fields takes additional time to review the patient history. Collaborating laboratories expressed a willingness to collect this and other data as part of time-limited research projects in collaboration with the ARSP (see Opportunities for improvement). Laboratories that are not currently participating agreed (2/3) that some of these data fields such as hospitalisation and vaccination status would be difficult to collect and may be a barrier to their participation.

Figure 7: Proportion of Australian Rotavirus Surveillance Program (ARSP) metadata submission form complete by data field, 2012 to 2022



* The hospitalisation data field was added in 2016, the Indigenous status data field was added in 2020, and the vaccination status field was added in 2022. Data relating to these fields was not collected before these years.

** The vaccination status field has not been completed by Victorian laboratories since this data field was added in 2022.

Area for improvement: New data fields tend to have poorer completeness. Respondents noted some of these data are not readily available and would require accessing patient records, which would increase the burden on collaborating laboratories.

Recommendations:

- The ARSP work with DH and collaborating laboratories to investigate options to either improve the completeness of epidemiological data (particularly vaccination status, hospitalisation status and Indigenous status) or utilise alternative methods of collecting this data. For example:
 - Integrating the ARSP data into PHESS may support data linkage to collect and analyse this information.
 - Collaborating laboratories have expressed willingness to collect this and other data as part of time-limited research projects.
 - DH has indicated they may be able to support surveillance for individuals aged <16 years via the Australian Immunisation Register to complete vaccination and Indigenous status checks.
- The ARSP engage collaborating laboratories about the addition of new data fields and the feasibility of collecting the data before implementing any changes. This will take into account the extra burden additional data collections can place on laboratories, and the subsequent disincentive to participate in the program.
- The ARSP to define the minimum dataset required for samples and identify fields that are optional.

Positive predictive value

Between 2012 and 2022, 75% (912/1216) of samples that proceeded to analysis tested positive for rotavirus. When asked about the rate of false positives from diagnostic laboratories, MCRI advised it was higher than expected. The positive predictive value has varied but generally increased over time from a low of 30% (11/37) in 2016 to a peak of 93% (170/183) in 2022 (Figure 6). MCRI advised that this variation and improvement over time may be due to changes in diagnostic assays used by collaborating laboratories, as these assays have different specificity and sensitivity. Investigation of each assay used by collaborating laboratories was beyond the scope of this evaluation.

MCRI noted that diagnostic laboratories have moved away from ELISA based methods to qPCR. Initially, the guidelines around the cycle threshold (Ct) value³ cut-offs for qPCR were limited and laboratories were using their own cut-offs, which were often too high. By comparing diagnostic laboratory data to MCRI data, MCRI was able to identify a realistic range that would better capture true positives. MCRI provided education on Ct values and partnered with diagnostic companies and RCH to provide a panel of rotavirus negative and positive samples to run additional testing to validate new assays. MCRI noted that certain laboratories had higher rates of false positivity when moving to new diagnostic assays, but that these issues were typically resolved within a year or two. MCRI also noted that another explanation for samples testing negative after a positive diagnostic test was that a batch of samples may be handled or stored incorrectly, leading to the samples degrading and the testing not being as sensitive. This is a rare occurrence but has happened in the past.

All respondents from collaborating laboratories (3/3) emphasised that receiving confirmatory results of rotavirus infection to understand the positive predictive value, and the rate of false positives was a very useful component of the ARSP, as it helped them identify issues in their own testing practices. As noted above, currently this feedback is not routinely provided to two of three collaborating laboratories, however MCRI advised that this could be provided if collaborating laboratories were interested in this information.

Recommendations:

- The ARSP routinely report samples identified as 'rotavirus negative' back to collaborating laboratories.
- The ARSP monitor the positive predictive value of samples, to quickly identify increases in false positives or other anomalies with collaborating laboratories and feedback information back to the affected laboratory as soon as possible. This will support the continuous improvement of diagnostic laboratory testing.

³ The cycle threshold (Ct) is the number of amplification cycles required for the fluorescent signal generated by the reaction to cross a predefined threshold where the instrument declares the test to be positive. Lower Ct values indicate higher levels of rotavirus in the sample.

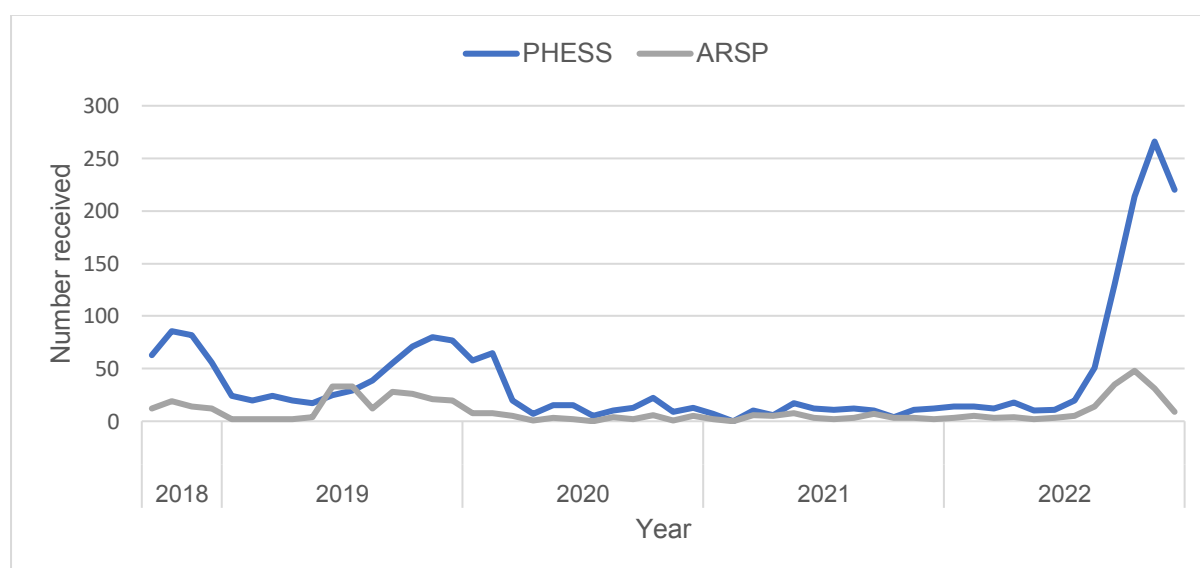
Sensitivity

Sensitivity to detect rotavirus and rotavirus genotypes

The ARSP is not a diagnostic program. Therefore, it was not relevant to assess the ability of the program to detect rotavirus cases in the community. The sensitivity and specificity of the laboratory assays used by the ARSP were not investigated as part of this evaluation. The laboratory assays are regularly reviewed by the ARSP as part of a process of quality assurance and are considered to be gold standard.

The ARSP aims to characterise rotavirus genotypes causing disease, including identifying new genotypes and understanding changes in genotypes due to the introduction of the rotavirus vaccination program. Since rotavirus became notifiable in Victoria, a total of 2112 cases (confirmed Victorian cases and interstate cases) have been notified to DH between September 2018 and December 2022 by Victorian laboratories, and 23% of these (493 positive samples) have been analysed by the ARSP. The number of samples sent to the ARSP increases when there is an increase in notified cases, however generally a greater proportion of samples appear to be sent to the ARSP when there is a lower incidence of cases (Figure 8).

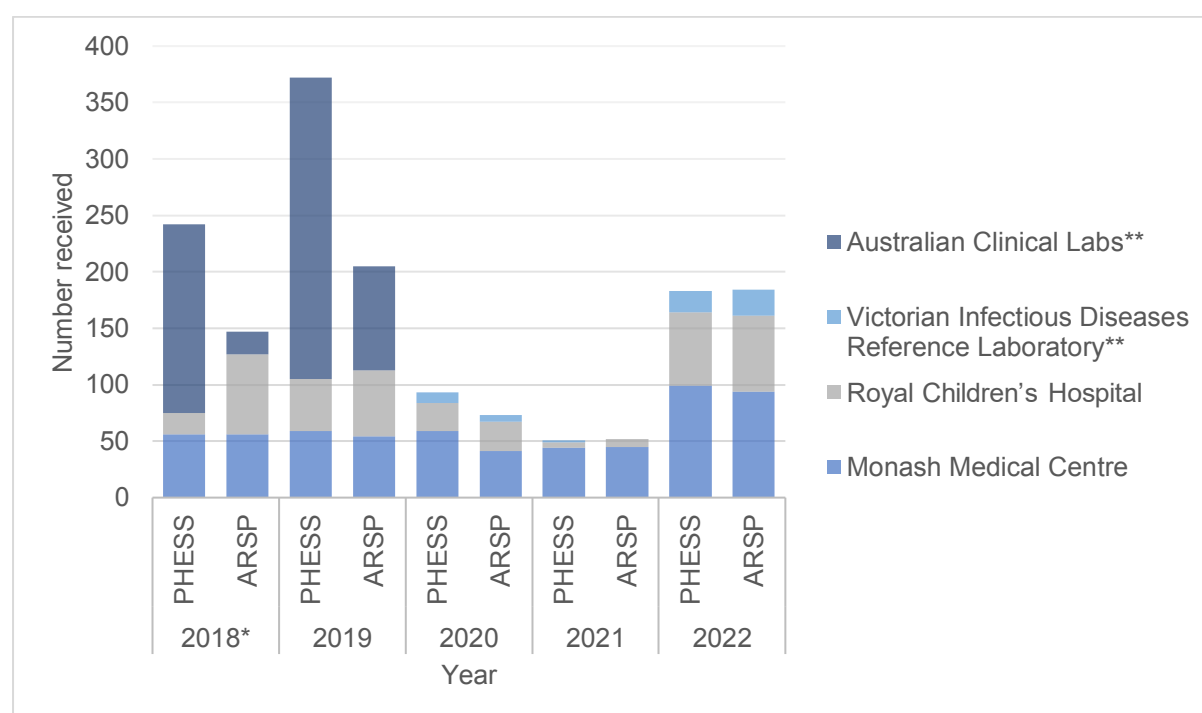
Figure 8: Number of rotavirus cases notified by Victorian laboratories as recorded in the Victorian Public Health Event Surveillance System (PHESS) compared to number of positive samples from Victorian laboratories analysed by the Australian Rotavirus Surveillance Program (ARSP), by month and year from September 2018



Respondents from collaborating laboratories (3/3) advised they routinely send all positive rotavirus samples to the ARSP. This was broadly validated by PHESS data, with strong

alignment for the years when collaborating laboratories were contributing, with the exception of ACL, which no longer contributes (Figure 9). For the collaborating laboratories currently contributing, each laboratory sends more than 90% of its positive samples to the ARSP. Of note, RCH has sent a slightly higher number of samples to the ARSP than it has notified to DH every year, suggesting that some of these samples may be from interstate and thus have not been notified. This in turn may mean the total number of rotavirus cases included in the PHESS dataset may be an undercount of positive samples tested at Victorian laboratories.

Figure 9: Number of rotavirus cases notified by Victorian laboratories as recorded in the Victorian Public Health Event Surveillance System (PHESS) compared to number of positive samples from Victorian laboratories analysed by the Australian Rotavirus Surveillance Program (ARSP), by laboratory for collaborating laboratories, 2018 to 2022



* In 2018, ARSP data includes all positive samples analysed throughout the year, however PHESS data only includes cases reported from September onwards.

** Data for each year is only shown for laboratories that reported to both DH and the ARSP for that year. ACL data is only shown for 2018 and 2019 and VIDRL data is only shown for 2020, 2021 and 2022, when these laboratories were collaborating with the ARSP.

From 2012 to 2022, genotyping and characterisation has been successfully completed for all rotavirus samples in Victoria, with results classified as 'Wildtype G1P[8]', 'Non-vaccine strains (including with G1P[8])' or 'vaccine-like'. It cannot be determined with certainty how sensitive the ARSP is for detecting the emergence of new genotypes, as it is the only system within Australia currently collecting this information. However, MCRI noted that every effort is made

to detect new variants. The low number of non-typeable samples suggests that new genotypes are not being missed and non-typeable samples are sequenced to support identification of new genotypes.

The ARSP regularly reports on changes in genotype trends, including the dominant strain detected in each state, and the emergence of new and uncommon genotypes in prior annual reports, such as the unexpected emergence of G12P[8] in 2012, the decrease of G1P[8] in the vaccine era, and the emergence of G8P[8] as a predominant strain in 2021. These trends are often observed across multiple Australian states and territories rather than isolated to a specific region. The ARSP has also been amongst the first to describe a number of newly emerging genotypes such as equine-like G3P[8].

Sensitivity to detect rotavirus outbreaks

MCRI respondents (2/2) noted that whilst they do not detect outbreaks, they may have a role in identifying *“a predominance of a genotype suggesting an outbreak, or indications of epidemiologically linked cases that might otherwise not have been linked”*. Respondents from all groups (n=4) advised that the ARSP has never detected an outbreak that has not already been referred to them by a collaborating laboratory or DH.

Most gastrointestinal outbreaks in Victoria do not have samples associated with the outbreak (either samples were not collected or no pathogen detected in samples that were collected). From 2018 and 2022 there were 2274 outbreaks recorded in PHESS which were classified as ‘Viral (not laboratory specified)’ or ‘Foodborne not further specified’. It is likely that some of these would have been due to rotavirus. Within this timeframe there were 24 confirmed rotavirus outbreaks recorded in PHESS, with most occurring in ACFs (n=10) and childcare facilities (n=10).

The ARSP were not able to provide data on the number of outbreaks the program had supported in Victoria, however the annual report from 2020 noted that the ARSP assisted in two small outbreaks in Victoria, with a total of fourteen associated cases.

Area for improvements:

- The ARSP does not collect detailed data on the number of outbreaks they support or the outbreak samples analysed by the program.
- Most gastrointestinal outbreaks recorded in PHESS do not have an organism or cause identified due to a lack of laboratory testing or no pathogen being detected. Therefore, it is unclear how many rotavirus outbreaks occur within Victoria.

Recommendations:

- The ARSP to consider collecting additional data on the total number of outbreaks they support and total number of outbreak cases analysed by the program.
- DH to conduct an evaluation of the gastrointestinal outbreak surveillance system in PHESS, considering a substantial proportion of outbreaks are not specified.

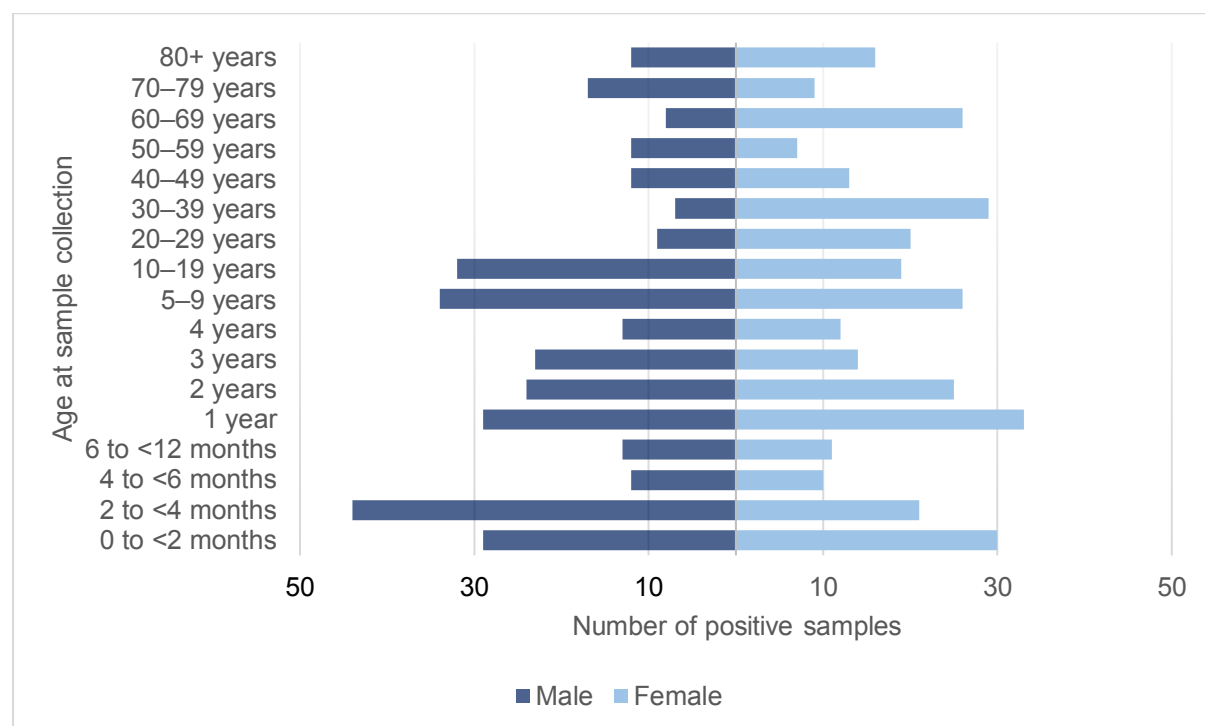
Representativeness

Age and sex

Respondents from DH (n=2), MCRI (n=1) and collaborating laboratories (n=2) expressed concern that adult cases may be under-represented in the ARSP, particularly as one of the collaborating centres is a paediatric hospital. The results show that the ARSP was broadly representative of notified cases in terms of age and sex (Figure 10A and 10B). The ARSP dataset was slightly skewed towards infants <1 years old compared with PHESS data for Victoria (26% compared with 18% respectively). However, in other childhood age groups representation was approximately the same, with 27% of cases in both ARSP and PHESS aged between 1 – 4 years, and 17% cases in the ARSP and 15% in PHESS aged between 5 – 19 years. Adults were slightly underrepresented in the ARSP dataset compared with PHESS (30% and 40% respectively). As one of the three collaborating centres in Victoria is a paediatric hospital, recruitment of additional collaborating centres is the only likely method of increasing the representativeness of adult rotavirus samples from Victoria into the ARSP. The ARSP was representative by sex, with 51% of samples reported as male and 49% as female in ARSP dataset, compared with 48% reported as male and 52% as female in PHESS.

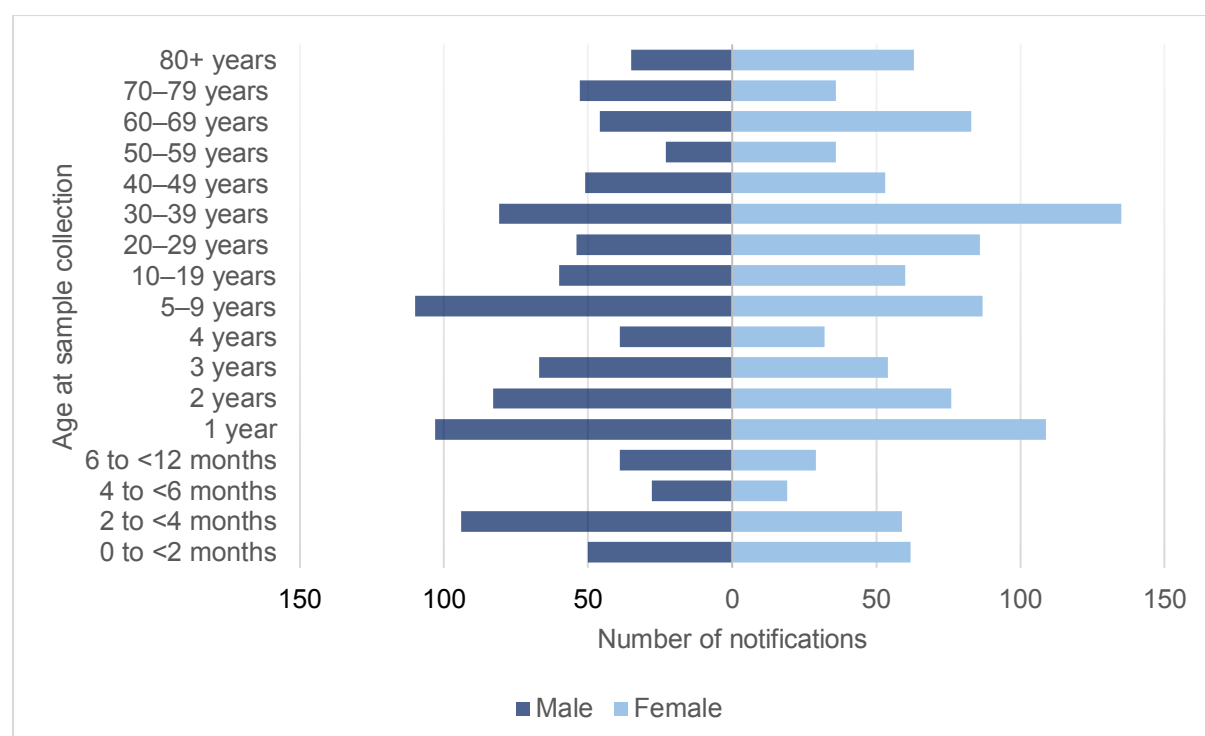
Strength: The ARSP is broadly representative of notified cases in Victoria by age and sex.

Figure 10A: Age and sex of rotavirus positive cases* analysed by the Australian Rotavirus Surveillance Program, 2018 to 2022



* Reported by Victorian laboratories only

Figure 10B: Age and sex of rotavirus positive case notifications* in the Victorian Public Health Event Surveillance System, 2018 to 2022



* Notified by Victorian laboratories only

Geography

To understand the geographic representativeness, the residential LGA for ARSP positive samples were compared with the residential LGA for notified cases for the years 2018 to 2022 (Figure 11A and 11B). A substantial proportion of LGAs in rural and regional Victoria were not represented in the ARSP dataset (20 of 47 rural and regional LGAs with zero samples) (Figure 11A). These regions tended to have a lower incidence of notified rotavirus cases (Figure 11B), with only three of the LGAs with no samples in the ARSP having ≥ 10 cases notified and recorded in PHESS (Latrobe, Moorabool and Wodonga LGAs).

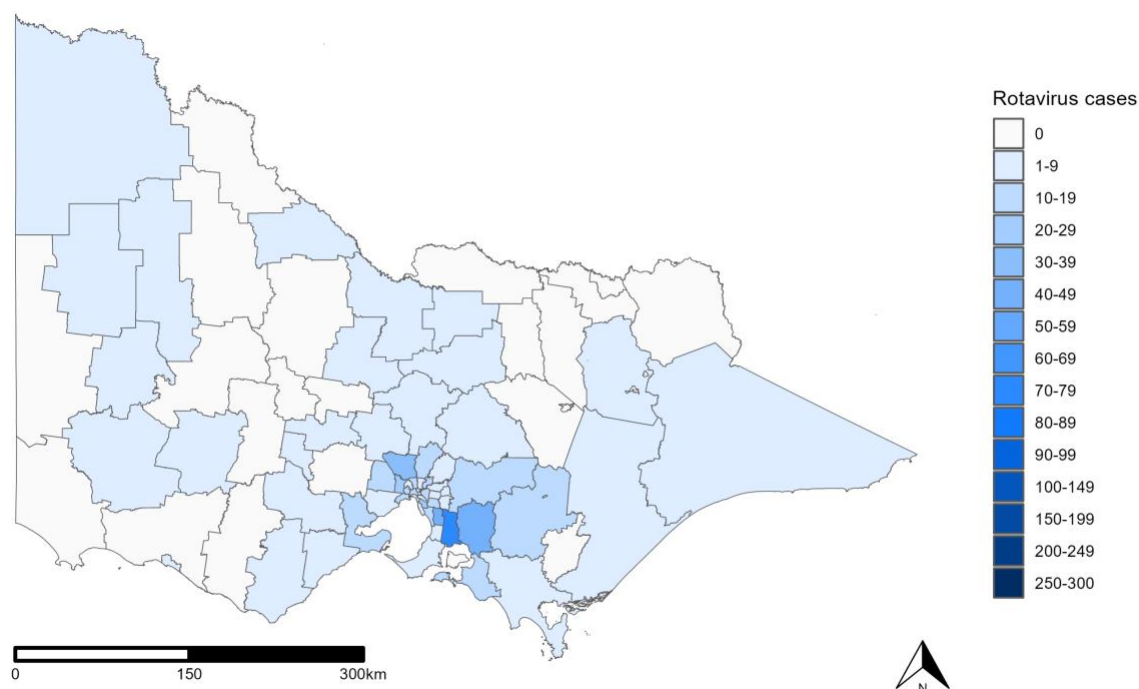
Overall, in 59% (47/79) of LGAs the ARSP data reflected $\geq 10\%$ the number of notified cases in PHESS. There were some notable discrepancies between the datasets in LGAs with regional cities, with $\leq 10\%$ of notified cases from Greater Bendigo, Greater Shepparton and Ballarat represented in the ARSP data (4/48 cases, 2/24 cases, and 1/46 cases respectively). In metropolitan Melbourne, the proportion of notified cases represented by ARSP data was generally much higher compared with regional areas. However, there were still some discrepancies in the LGAs located in the south-west of Melbourne, with Wyndham (8 samples in the ARSP compared with 141 notified cases) and Greater Geelong (10 samples in the ARSP compared with 206 notified cases) being particularly under-represented.

The ARSP dataset included a greater proportion of interstate samples (14%, 72/503) compared with notified cases in PHESS (2%, 34/2099). This is likely due to the fact Victorian laboratories may not be notifying all interstate cases to DH.

Area for improvements:

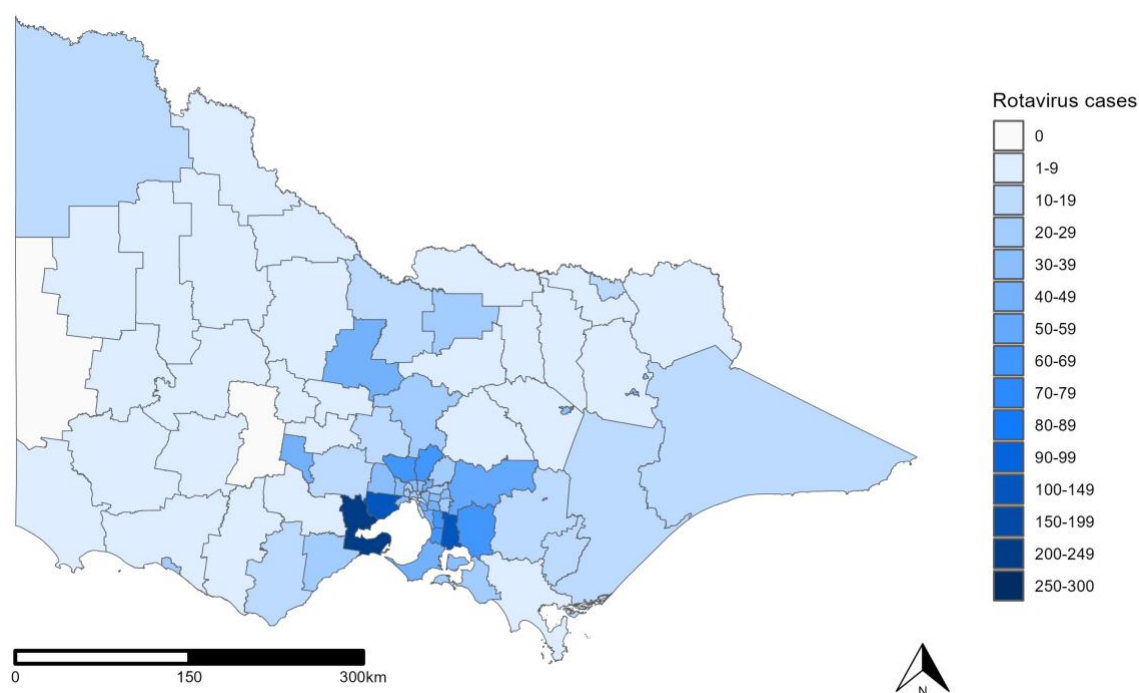
- Some regions in rural Victoria are not represented in the ARSP data, and some regional cities are underrepresented.
- Some regions in and near metropolitan Melbourne are underrepresented, particularly south-west of Melbourne and the city of Geelong.

Figure 11A: Number of positive rotavirus cases* analysed by the Australian Rotavirus Surveillance Program, by residential Local Government Area in Victoria, 2018 to 2022



* Reported by Victorian laboratories only

Figure 11B: Number of positive rotavirus cases* notified to the Victorian Public Health Event Surveillance System, by residential Local Government Area in Victoria, 2018 to 2022



* Notified by Victorian laboratories only

Opportunities for improvement

Respondents across all groups (n=4) had expressed concern that the samples analysed by the ARSP may not be representative of rotavirus cases in Victoria. The cause for these concerns stemmed from collaborating laboratories all being based in metropolitan Melbourne and primarily catering to children, with one of three collaborating laboratories located in a paediatric hospital. MCRI noted that the program is restricted by which laboratories were collaborating, and that this could influence the representativeness of the sample, particularly in terms of age and geography. Respondents made a few suggestions of ways in which the ARSP could become more representative (Box 4).

Box 4: Suggestions on how to improve the representativeness of samples analysed by the Australian Rotavirus Surveillance Program (ARSP)

- Recruit additional collaborating laboratories that have collection centres that are based in rural and regional Victoria (n=3)
- Conduct statistical analyses to determine the optimal sample size required to get a representative sample within Victoria and work towards this as a threshold for the state (n=1)
- Improve the collection of hospitalisation data to better understand the proportion of cases that are hospitalised or in the community (n=1)
- Coordinate a 'snapshot' study where all rotavirus samples from across the state for one day are sent to the ARSP for genotyping (n=1)

Recommendations:

- The ARSP target laboratories based in rural and regional Victoria and south-west Melbourne and Geelong, to be recruited as collaborating laboratories.
- The ARSP continue to encourage new collaborating laboratories to send all rotavirus samples to the program. Where this is not possible, the ARSP to provide the laboratories with information on selecting a representative sample which includes adult rotavirus cases.
- The ARSP seek statistical advice on defining geographical representative sample sizes required for the state of Victoria and include this as a performance indicator of the program.

ARSP level of usefulness

State-wide surveillance

Just over half of all respondents agreed (n=6) that the ARSP would be most useful if individual results (i.e. results from each sample) were regularly provided to collaborating laboratories and DH.

Some respondents from DH and MCRI (n=3) noted there is a need to improve communication between DH and the ARSP in order to be able to fully utilise the data and get “*full richness*” and “*maximum value*” out of the ARSP. Respondents from DH and MCRI (n=2) agreed that the inability to link results in PHESS is a major limitation in the usefulness of the ARSP. DH respondents (2/3) were open to working more closely with the ARSP to improve the usefulness of the system, with one noting a “*co-design process*” may identify how the program can best support state-wide surveillance and response to outbreaks. One MCRI respondent noted that there are components of the program that DH may not be aware of, and that in depth conversations would support identifying how the ARSP can best work with DH to support state-wide surveillance.

The ARSP is perceived as most useful by collaborating laboratories when they are regularly receiving results from the samples they contribute (3/3). One laboratory is already receiving most of their results, but others (2/3) advised they are not currently receiving all of their results. This was considered the most useful output from the ARSP by respondents across all groups (7/11), as it assists in validating diagnostic results (e.g. identifying false positives) and answering clinical questions for patients (e.g. whether strain is vaccine-derived). Respondents from collaborating laboratories (2/3) highlighted that receiving advice on what specific genotypes meant in terms of public health was also a useful output from the ARSP.

Policy and protocols

The ARSP is designed to be a national laboratory surveillance system. Whilst most respondents (7/11) suggested there was scope to support the state-wide understanding and management of rotavirus, three respondents felt that the program’s strengths were more prominent at a national level. This was particularly relevant to the program influencing rotavirus vaccination policy. Some respondents from DH (n=1) and MCRI (n=1) explained that unlike some other vaccination programs, rotavirus vaccinations are run through the NIP and “*there is limited control over [the vaccination program] at a state level*”. Consequently, the program is of little use in influencing state-wide vaccination policy but can impact national

policies for rotavirus. Respondents from DH (n=2) noted that few public health actions are currently taken in response to rotavirus cases and outbreaks in Victoria. However, respondents from DH (2/3) agreed that the ARSP annual reports might inform state-wide protocols for managing rotavirus, when these were updated in the future.

Supporting outbreak investigations

Currently the ARSP provides limited support to outbreak investigations in Victoria, with DH respondents (n=2) noting the results are unlikely to be useful when responding to most rotavirus outbreaks but may be useful if investigating a large or unusual outbreak within the state. MCRI respondents (2/2) advised that they had supported outbreak investigations in other jurisdictions and provided examples of how this had been useful, such as understanding whether the outbreak was related to a vaccine or a lack of vaccine and providing this information to support public messaging. A collaborating laboratory noted that genotyping of all cases in rotavirus outbreaks would be very valuable not only for immediate outbreak responses but also for improving Victoria's understanding of the dominant genotypes and causes of rotavirus outbreaks. Improving collaboration and communication between stakeholders may lead to the ARSP data being better utilised during outbreak investigations within Victoria.

Usefulness of the ARSP annual reports

Most respondents who were aware of the ARSP annual reports regularly read them (5/8), but agree this is mostly for interest, and that the annual reports do not influence their day-to-day work. Some respondents (4/11) including all non-collaborating laboratories (3/3) do not read the annual reports, with the primary reason for this being a lack of awareness that they are publicly available. Once these respondents were aware where the annual reports are published, they indicated they wanted to read them to better understand rotavirus genotypes in Australia. Respondents from laboratories and DH (n=4) suggested that there should be a process to subscribe to annual reports so they are received in a timely manner, with some collaborating laboratories (2/3) noting they have not been receiving reports recently and thought that the ARSP should be sending these as a "*common courtesy to collaborators*". Some respondents from DH (n=1) and collaborating laboratories (n=1) felt that a state-wide annual report may be more useful than a national report so that laboratories could compare their results across the state.

Recommendations:

- The ARSP establish a function whereby stakeholders can 'subscribe' to receive annual reports.
- The ARSP and DH meet to discuss how the ARSP can better support outbreak investigations in Victoria, including the type of reporting available in these circumstances, and how this has been utilised in other jurisdictions.

Opportunities for future improvement

Short-term opportunities to improve the ARSP and our understanding of rotavirus in Victoria (recommended to occur within 2 – 3 years)

Respondents from MCRI and DH (n=3) agreed that providing individual data to DH on genotyping results would allow for integration of the data into PHESS. This would support DH to conduct data linkage projects using PHESS and other data sources (e.g. the AIR) to answer a range of specific research questions. MCRI advised that this kind of data linkage has successfully been undertaken in Western Australia and the Northern Territory. DH and MCRI respondents (n=2) were open to working collaboratively to facilitate this process, which would enable them to work together to undertake analyses and produce research outputs. Respondents perceived this as a key opportunity to enhance the usefulness of the ARSP within Victoria.

Many respondents (n=5) also raised a number of specific research questions they had, that they believed could be answered by the ARSP through collaborative research projects (Box 5). Respondents noted that answering these research projects would both enhance our understanding of rotavirus epidemiology in Australia, in line with the ARSP's objectives, and would also provide opportunities to improve engagement with collaborating laboratories who could participate in research outputs (n=3). The ARSP is already conducting research on some of the identified research themes and have indicated they would consider incorporating a feedback mechanism on this research to keep collaborators abreast of work in progress.

Box 5: Themes for research that respondents felt should be conducted by the Australian Rotavirus Surveillance Program (ARSP)

- The impact of vaccine pressure on the epidemiology of rotavirus (n=2)
- Vaccine effectiveness and vaccine escape (n=2)
- Where rotavirus strains are originating and how travel influences the epidemiology of rotavirus (n=2)
- Research to support the introduction of new vaccines (n=1)
- Understanding vaccine-related strains and emerging strains (n=2)

Longer term system improvements that may be considered (recommended to occur within 5+ years)

Respondents raised a few key suggestions of ways in which the ARSP could be enhanced in the longer term.

Respondents noted that the ARSP does not conduct whole genome sequencing of rotavirus samples, with some from MCRI and collaborating laboratories feeling this was a gap in the program (n=3). Respondents highlighted that sequencing data would allow the program to better assess relatedness between strains, the origin of unusual strains, molecular epidemiology and transmission dynamics. An MCRI respondent noted that they had the capability to conduct sequencing, but do not currently have the funding or resources to do this routinely.

Some respondents (n=3) also suggested that there may be an opportunity to expand the ARSP beyond a standalone system for rotavirus into a broader gastrointestinal surveillance system. Respondents considered it would be useful to commence collecting typing and sequencing information on a range of pathogens, such as norovirus, to gain baseline data ahead of potential future vaccines being implemented. An MCRI respondent noted there would need to be some development of the program for this to occur, and this wouldn't be feasible without additional funding. One respondent from a collaborating laboratory suggested it may be possible to integrate the ARSP into other surveillance systems, such as the WHO Collaborating Centre for Reference and Research on Influenza, to share expertise and resources which may support program expansion.

DISCUSSION

The ARSP is the only surveillance system within Australia to focus on characterising rotavirus strains and plays an important role at a national level in informing rotavirus policy and vaccination programs. In Victoria, the role of the program is less well defined, and the ARSP has no specific objectives at a state-wide level. However, this evaluation demonstrates that the ARSP actively seeks to contribute to rotavirus surveillance at a jurisdictional level, and has capacity to provide valuable insights into rotavirus genotypes, the impact of the rotavirus vaccination program, and rotavirus outbreak investigations.

This evaluation demonstrated that the ARSP is a relatively simple, acceptable and flexible system. The international standing, quality and accuracy of the data produced by the ARSP were seen as key strengths of the system (strengths and weaknesses are summarised in Appendix B).

This evaluation also highlighted some key limitations of the ARSP at a state-wide level. The ARSP is not well integrated into other state surveillance systems and individual results are not routinely provided to all collaborating laboratories, which limits the usefulness of the system within Victoria. There are some weaknesses in the stability of the surveillance system, with a need to enhance recruitment and retention of collaborating laboratories within Victoria, and whilst the samples appear to be broadly representative in terms of age and sex, there is a need to improve the geographic distribution of samples in Victoria. Whilst the ARSP aims to assist in the public health response to outbreaks, there were some key barriers to this which were also weaknesses in the system (Appendix B).

Recommendations have been made to address these weaknesses and improve the ARSP in the Victorian context into the future. This includes: targeting laboratories that are based in underrepresented regions and/or undertake extensive rotavirus testing to collaborate; improving integration of the ARSP with other surveillance systems in Victoria; and improving relations and incentives for collaborating laboratories to support their recruitment and retention. All recommendations are summarised in Appendix C.

There were several limitations in this evaluation. Although this evaluation focussed on the ARSP within Victoria, it was impossible to separate some components such as funding and resources from the broader national system. Only one laboratory that has previously collaborated with the ARSP is no longer collaborating in Victoria. This respondent may have provided valuable insights into barriers collaborating laboratories face when being involved in the ARSP but chose not to participate in this evaluation. The ARSP identifies Victorian

samples as those provided by Victorian laboratories, however PHESS data is based on Victorian residence. Cases that were classified as “not notifiable” in PHESS (i.e. interstate cases) were included in the analysis to try to make the datasets comparable. However, it is possible that some individuals with interstate addresses were not notified to DH leading to an undercount of positive samples tested at Victorian laboratories. The data suggests this applies to a small volume of cases but may have led to the sensitivity and representativeness of the ARSP being overestimated.

This evaluation supports a better understanding of the ARSP in Victoria and opportunities to improve the system locally in the future. Although this evaluation was targeted to the Victorian context, some findings and recommendations may be relevant in other states and territories and at a national level.

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APPENDIX A: SAMPLE INTERVIEW QUESTIONS

Background

- What are the objectives of the ARSP?
- What governance structures are used for the ARSP?
- What resources are required to operate the ARSP in Victoria (e.g. financing, personnel, laboratories)?
 - Who provides these resources?
 - Are these resources readily available?
 - Are there any barriers to access the required resources?
- What resources are required for the laboratory to participate in the ARSP (e.g. time, funding, FTE, consumables)?
- Do you provide any funding to support the ARSP?
 - If yes- can you disclose how much?
- Is there any scope to provide additional resources / funding in the future?

Stability

- How are the data collected, stored and analysed internally?
- Is there anything that would stop or prevent the ARSP from operating as intended?
 - Are all laboratories invited to participate in the ARSP actively participating?
 - Are laboratories who report to the ARSP consistently providing samples at the requested time intervals?
 - Do these time intervals vary between laboratories?
- How regularly is your lab able to participate/contribute to the ARSP? (e.g. always, every few months, occasionally)
 - If you are not able to regularly contribute, what barriers prevent this from occurring?
- In your opinion does the ARSP collect, manage and provide accurate data on rotavirus cases in Victoria?
 - If no, what do you believe are the factors that are affecting its ability to undertake these tasks?

Acceptability

- Are you willing to continue operating/supporting the ARSP into the future?
- In your opinion, how willing are laboratories to participate in the ARSP into the future?
 - What are some of the barriers ARSP faces with laboratories choosing to participate?
 - What does the ARSP do to support the laboratories to participate in the ARSP?
- Why does your laboratory choose to participate in the ARSP?
 - Is your laboratory willing to continue participating in the ARSP into the future?
 - If so why, if not why?
- Have you ever been requested to provide rotavirus samples to the MCRI for the ARSP?
 - If yes:

- If never participated – what were the barriers in sending positive samples to the ARSP?
 - If previously participated but no longer participating – why did you stop sending positive samples to the ARSP?
- If no, is this something that your laboratory may be supportive of contributing to in the future?
- Are there changes that would make you more supportive of participating in the ARSP?

Simplicity

- How are laboratories selected to participate?
 - Is there a minimum or maximum number that could be involved?
 - Do you see any benefit to including more laboratories?
- What is the capacity of the system, could more samples be analysed?
 - Is there a minimum or maximum number of isolates that can be received and processed?
 - Do you see any benefit to including more samples?
 - Is the system able to cope if more samples are sent on an ad hoc basis such as in an outbreak?
- What is the process for storing and sending samples to the ARSP?
- In your opinion is sending samples to the ARSP simple?
- On average, how much time is spent on the following activities:
 - Identifying samples to send
 - Packing samples
 - Arranging transportation of samples
 - Completing associated paperwork
- Are there any barriers or challenges to sending samples to the ARSP?
 - If so what are these?
- What kind of data do you receive from the ARSP?
 - How do you receive this data?
 - How do you use this data?
 - Is this data integrated into other systems (e.g. PHESS)?
 - If yes, please tell me what systems it is integrated into and how this occurs?

Representativeness

- How are samples selected to be sent to the ARSP?
- Does your laboratory process rotavirus samples?
 - Are these samples sent to any other laboratory for additional rotavirus testing?

Timeliness

- How regularly do laboratories/you provide samples? (e.g. as they occur, each quarter, depends on the lab)
 - Do you see any benefit to having laboratories provide samples at more frequent intervals?
- On average, how long does it take for a collaborating laboratory to send samples to MCRI after they confirm a positive rotavirus results?

- Once samples are received by MCRI, on average, how long does it take MCRI to analyse the sample?
- How often does MCRI provide genotyping results back to the reporting laboratory?
 - Do you collect any data on the timeframes for processing positive samples (e.g specimen collection date, specimen positive result date)?
 - Are there any points at which delays occur in receiving or analysing samples?
 - What factors can lead to delays in receiving and analysing samples?
- Do the discussed timeframes vary for samples being analysed as part of an outbreak?
 - If so, what are the average timeframes used for outbreak samples?
- Is there scope to increase the timeliness of reporting sample results?
- If available, how regularly would you like to receive reporting from the ARSP?
- How regularly do you receive information from the ARSP?
 - Have you ever requested more frequent information / reporting?
 - If yes, was the ARSP able to accommodate these requests?
 - If no, would you considering asking for this in the future?
 - In not why?
 - Has you ever requested ad hoc reports?
 - If so, was the ARSP able to accommodate these request?
 - If no, would you considering asking for this in the future?
 - In not why?

Data quality

- When your lab provides / when you receive samples and completes the accompanying form on the epidemiology of these samples:
 - How often is the epidemiological data complete? (e.g. for every case, some cases, no cases) / How complete is the accompanying epidemiological data (e.g. always complete, usually complete, often incomplete)
 - Does your laboratory review the completeness of the epidemiological data is? How accurate is the accompanying epidemiological data (i.e. any discrepancies)?
 - If you laboratory is unable to collect epidemiological data for samples, what impedes this?
 - Are there any gaps in the data you receive?
 - If so, how does this impact the ARSP analysis reporting for Victoria?
- Does the ARSP receive enough information from laboratories to be useful for the analysis and reporting of rotavirus in Victoria?

Flexibility

- Can the ARSP be scaled up and down easily to cope with a surge in laboratory samples coming through?
- Can you easily change variables collected in the systems?
 - Can the systems be adapted to incorporate new data variables if requested by stakeholders?
- Are there restrictions on what data you can collect, analyse, or report?
- Is there scope to increase the number of samples your laboratory sends to the ARSP?
 - Is there scope to increase the frequency of sending samples to the ARSP?

- Is there capacity/capability to do additional in-house testing and sub-typing of rotavirus samples at your lab?
 - Is this something your laboratory would be supportive of doing in the future?
- Have changes to the ARSP surveillance system occurred in the past?
 - If so, how many times have these occurred and why have these changes been implemented?
 - Are you able to provide an example of a recent change and how successful it was?

Sensitivity

- What role does the ARSP play in identifying and supporting public health responses to rotavirus outbreaks?
 - Has the ARSP ever identified a previously unrecognised outbreak?
- Has the ARSP ever detected a previously unrecognised outbreak of rotavirus in Victoria?
 - If so, how did they alert DH of the identified outbreak(s)?
- What role does your lab play in identifying and supporting public health responses to rotavirus outbreaks?

Usefulness

- Who receives data from the ARSP and in what format?
 - What data are reported to state and national bodies (e.g. Commonwealth, ATAGI, JIC)?
 - What data are reported to external bodies (e.g. GSK)?
- How do you think the data from the ARSP is used in Victoria? Do you use the data provided by the ARSP for rotavirus surveillance in Victoria?
 - If yes, how does this data support rotavirus surveillance and response in Victoria?
 - If no, why is this data not used by DH?
- Do you read any of the ARSP annual reports that are published? Do you receive any other data or reports from the ARSP?
 - If so, how do you use this to inform your work?
 - If not, is this something that you would like to receive in the future and if so, how might it support your work?
- In your opinion, do you think the ARSP informs policy and vaccine strategies?
 - Are there any examples you know of when ARSP data has been used to support public health action?
- What do you think are the strengths of the ARSP in undertaking rotavirus surveillance in Victoria?
- What do you think are the weaknesses of the ARSP in undertaking rotavirus surveillance in Victoria?
 - Can you elaborate on what could be improved?
- How useful is the information you receive for your work?
 - Would you like to receive more information? If so what other type of information would you need?

APPENDIX B: SUMMARY OF STRENGTHS AND WEAKNESSES

THEME	STRENGTHS	AREAS FOR IMPROVEMENT
Confidence in the quality and accuracy of the ARSP	• Respondents noted that the historical standing of the program was relatively unique to Australia. The program has published over 20 years of annual reports, providing a strong evidence base to inform policy and research. • The ARSP processes are easy to follow. The program is seen as simple and cost-effective. • The ARSP is well respected with a strong international reputation for excellence. Respondents have confidence and trust in the way the program is run and the accuracy of the data it produces. • The ARSP has successfully genotyped all Victorian samples included in the analysis over the past decade.	• New data fields tend to have poorer completeness. Respondents noted some of these data are not readily available and would require accessing patient records, which would increase the burden on collaborating laboratories.
Ability of the ARSP to continue operating into the future		• The ARSP is reliant on collaborating laboratories to operate, however it is challenging to attract and retain collaborators, with Australian Clinical Labs (ACL), a major laboratory for rotavirus, no longer contributing to the ARSP. • The ARSP funding model prevents collaborating laboratories from being provided with reimbursement or financial incentive to participate.
Ability of the ARSP to support outbreak investigations in Victoria	• The ARSP prioritises samples of public health importance associated with outbreaks throughout the year and can produce <i>ad hoc</i> reporting to support outbreaks if required.	• Results during outbreaks can take up to two weeks to process. This limits the utility of the information during an outbreak response. • The ARSP does not collect detailed data on the number of outbreaks they support or the outbreak samples analysed by the program.

		Most gastrointestinal outbreaks recorded in PHESS do not have an organism or cause identified due to a lack of laboratory testing or no pathogen being detected. Therefore, it is unclear how many rotavirus outbreaks occur within Victoria.
Whether the ARSP presents representative data	The ARSP is broadly representative of notified cases in Victoria by age and sex.	- Some regions in rural Victoria are not represented in the ARSP data, and some regional cities are under-represented. - Some regions in and near metropolitan Melbourne are under-represented, particularly south-west of Melbourne and the city of Geelong.
Integrating the ARSP data into data from other Victorian surveillance systems		The ARSP is not integrated with other rotavirus surveillance systems in Victoria, particularly PHESS. This makes it harder to understand the results in the Victorian context and limits the utility of the data.

APPENDIX C: SUMMARY OF RECOMMENDATIONS

THEME	RECOMMENDATIONS
Governance, resourcing and staffing for the ARSP	• The ARSP to regularly review and document objectives for the program, in collaboration with their funders (at least every 5 years and when major changes in rotavirus surveillance occur). This will inform future priorities for the program and ensure objectives of the system are meeting the changing requirements of rotavirus surveillance. • The ARSP explore with current funders the ability to initiate longer term funding terms or seek additional funding from other providers to improve the security and stability of the program.
Integrating and linking the ARSP with other data	• DH and the ARSP should work together to develop a material transfer agreement to support the sharing of line listed data. • DH and the ARSP work together to identify a pathway to integrate genotyping data into PHESS. This could be achieved by the ARSP providing line listed data with laboratory ID directly to DH, or by the ARSP routinely reporting results to collaborating laboratories, who can then provide updated results to DH. • The ARSP routinely provide results and outcomes of all rotavirus samples back to collaborating laboratories (whether positive or negative and genotype). • The ARSP to provide outcomes of rotavirus samples back to collaborating laboratories (i.e. line-listed data) more frequently, for example quarterly once all analyses for a batch are complete.
Engaging and supporting collaborating laboratories to participate in the ARSP in Victoria	• The ARSP formally acknowledge all collaborating laboratories and personnel involved in the program in all research outputs. • The ARSP invest in engaging new collaborating laboratories in Victoria and build upon relationships with existing collaborating laboratories, by providing more regular updates on the ARSP and opportunities to be more involved. • The ARSP consider implementing low-cost options to improve the acceptability of the program for collaborating laboratories (see Box 3). • The ARSP seek additional funding to provide a nominal amount of financial reimbursement to collaborating laboratories. • The ARSP assess the feasibility of receiving metadata in other formats such as data extracts from laboratory systems or setting up a database in a system such as REDCap that the laboratories can use to transmit data. If there are no ethical or governance barriers to this approach, this should be accepted to minimise the time commitment required from collaborating laboratories. • The ARSP review current documentation for collaborating laboratories to ensure clear instructions on minimum data are incorporated.

	• The ARSP consider opportunities for both collaborating laboratories and other stakeholders such as DH to be involved in research outputs and publications, ensuring all collaborating laboratories have equal opportunities to be involved. • The ARSP offer laboratories the option of sending samples at a higher frequency (i.e. monthly) to encourage new laboratories to collaborate. • The ARSP prioritise re-engaging Australian Clinical Labs (ACL) in the program. • DH promote the ARSP to all laboratories undertaking rotavirus diagnostic testing at its internal discussions and relevant forums, including providing opportunities for the ARSP to present on the program. • DH offer support to the ARSP to engage new collaborating laboratories, by providing the ARSP with information on laboratories conducting rotavirus testing in Victoria, and the appropriate contacts from these laboratories. • DH facilitate the ARSP to present on the program at an appropriate forum such as a laboratory liaison meeting (a regular meeting convened by DH with Victorian laboratories) to build awareness of the program and demonstrate DH's support. • DH facilitate introductions to laboratories where appropriate.
Engaging all stakeholders and ensuring the usefulness of the ARSP	• The ARSP to consider providing regular informal state-wide reporting to all partners within Victoria (e.g. quarterly or bi-annually). This could be done via email or a regular meeting, providing an overview of high-level trends being observed and to keep stakeholders engaged in the program. • The ARSP establish a function whereby stakeholders can 'subscribe' to receive annual reports.
Managing and supporting outbreak investigations in Victoria	• DH liaise with VIDRL and formalise arrangements for all outbreak samples to be sent to the ARSP for genotyping, following VIDRL testing. The DH outbreak identifier should be sent with all samples to allow results to be linked back to PHESS as outlined above. • DH update outbreak investigation protocols for rotavirus outbreaks, emphasising the importance of sample collection, detail the recommended minimum numbers of samples needed for an outbreak, and rapid transport to VIDRL. • DH to update rotavirus outbreak management protocols to emphasise the importance in the timely collection of samples and sending to VIDRL for analysis. This should include recommended target timeframes. • DH to conduct an evaluation of the gastrointestinal outbreak surveillance system in PHESS, considering a substantial proportion of outbreaks are not specified. • The ARSP and DH meet to discuss how the ARSP can better support outbreak investigations in Victoria, including the type of reporting available in these circumstances, and how this has been utilised in other jurisdictions. • The ARSP continue to keep abreast of developments in new methodologies and technologies with the potential to speed up the processing of samples, particularly during an outbreak investigation.

	• The ARSP to consider collecting additional data on the total number of outbreaks they support and total number of outbreak cases analysed by the program.
Ensuring data quality and representativeness of the ARSP in Victoria	• The ARSP work with DH and collaborating laboratories to investigate options to either improve the completeness of epidemiological data (particularly vaccination status, hospitalisation status and Indigenous status) or utilise alternative methods of collecting this data. For example: ○ Integrating the ARSP data into PHESS may support data linkage to collect and analyse this information. ○ Collaborating laboratories have expressed willingness to collect this and other data as part of time-limited research projects. ○ DH has indicated they may be able to support surveillance for individuals aged <16 years via the Australian Immunisation Register to complete vaccination and Indigenous status checks. • The ARSP engage collaborating laboratories about the addition of new data fields and the feasibility of collecting the data before implementing any changes. This will take into account the extra burden additional data collections can place on laboratories, and the subsequent disincentive to participate in the program. • The ARSP to define the minimum dataset required for samples and identify fields that are optional. • The ARSP routinely report samples identified as 'rotavirus negative' back to collaborating laboratories. • The ARSP monitor the positive predictive value of samples, to quickly identify increases in false positives or other anomalies with collaborating laboratories and feedback information back to the affected laboratory as soon as possible. This will support the continuous improvement of diagnostic laboratory testing. • The ARSP document the process for sample selection, in the event more samples are received than can be analysed in a year. • The ARSP target laboratories based in rural and regional Victoria and south-west Melbourne and Geelong, to be recruited as collaborating laboratories. • The ARSP continue to encourage new collaborating laboratories to send all rotavirus samples to the program. Where this is not possible, the ARSP to provide the laboratories with information on selecting a representative sample which includes adult rotavirus cases. • The ARSP seek statistical advice on defining geographical representative sample sizes required for the state of Victoria and include this as a performance indicator of the program. • The ARSP to commence collecting data on the date samples arrive and the date the sample is analysed to allow for the timeliness of the ARSP to be assessed in the future.

CHAPTER V

**INVESTIGATIONS OF OUTBREAKS
AND ACUTE PUBLIC HEALTH
EVENTS**

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PROLOGUE

Study rationale

There are two components to this chapter. In Part A, I present a series of imported measles cases that occurred following reopening of the international border after the COVID-19 pandemic. Measles requires an extensive public health response and there is an ongoing risk of resurgence. I report a case series with lessons learned to support future local and national investigations. In Part B, I present an investigation of a vaccine cold chain breach (CCB) that occurred in a health facility in Victoria in 2023. I outline the approach to the investigation and highlight the importance of continual improvement in vaccine storage and management. Due to the sensitive nature of this investigation, specific details about the CCB (including the dates of the event) have been removed to ensure confidentiality of those affected, and meet commercial in-confidence requirements between the Department of Health, the Commonwealth Department of Health and Aged Care and vaccine suppliers.

My role

Part A includes the investigations and findings from four separate measles investigations. For each investigation, I was on the incident management team (IMT) and my role typically involved notifying contacts, checking their immune status, and advising on serological testing or post-exposure prophylaxis. I also supported flight contact tracing and coordinated with the National Incident Centre on international exposure sites. I responded to requests for information from international and interstate public health agencies and monitored the progress of the investigation, reporting on cases during Victoria's weekly surveillance meeting.

For the vaccine CCB described in Part B, I supported the IMT by coordinating meetings and contributing to briefings and the IMT action plan. I compiled the line list of impacted patients using data from the Australian Immunisation Register, set up a process for the health facility to report to the Department of Health, and undertook quality assurance of data. I also assisted in development of notification letters and frequently asked questions (Appendix A) for the health facility to send to impacted patients.

In addition, I contributed to several other outbreak investigations during my MAE program (see Chapter 3 and Chapter 7).

Lessons learned

There was a dearth of outbreaks during my MAE making it difficult for me to meet this competency. I was consequently involved in many early investigations that did not develop

into large outbreaks (Chapter 7). This meant that I was able to gain experience across a wide range of outbreaks and public health incidents across a breadth of disease. This showed me how different the response to different pathogens can be, but also affirmed that these core skillsets – identifying and defining the outbreak, conducting an investigation and determining the source, applying control and prevention measures, and implementing lessons to prevent future outbreaks – can be applied in any setting. My practical experience taught me that there is often no clear right or wrong approach, the response team is often working with limited information and making the best decision available. This showed me the value of being flexible and adaptable, and adjusting plans rapidly and efficiently in response to new information.

In each incident, I gained new skills and experienced different challenges. For example, in one investigation I needed to use language translators which made it difficult to ensure the message had been received and understood. In another investigation, the case's family became frustrated with the medical care received within Australia and there was a need to build rapport to get engagement. These experiences highlighted the importance of tailoring communications for culturally and linguistically diverse populations to implement effective control measures.

Finally, as I have mentioned, public health is like a team sport. Outbreak investigations can be stressful and intense and there is a need to work well within a team setting. The team was often multi-disciplinary and sometimes multi-agency, and there was a need to recognise the unique skills and experience each person brought to optimise the response. I learned the importance of offering my help and using other skills that I had that went beyond the typical 'epidemiology' skillset. It was also important to learn to be uncomfortable; I needed to be unafraid to admit when I didn't know something but also have the confidence to step into new roles to support these investigations. This helped me build strong relationships with the team.

Public health implications

In Part A, the public health response to measles cases resulted in no onwards transmission occurring within Australia. The case series was published in [Communicable Diseases Intelligence](#) and is reproduced in full in this chapter. The publication outlining lessons learned provided a useful overview of recent responses that could be applied across Australia to help maintain elimination of endemic measles transmission, and supported the transition of measles control activities to the new networked public health system. In Part B, the vaccine CCB investigation supported the health facility to improve their vaccine storage and management, to prevent future breaches. This investigation also helped the Department of

Health to improve internal practices for managing CCBs, given these are of increasing concern within the state.

Acknowledgements

Firstly, I would like to thank all of the epidemiologists and surveillance officers in the Communicable Disease Epidemiology and Surveillance unit (CDES), public health officers from the Communicable Disease Prevention and Control unit (CDPC) and public health medical officers for their time and effort training me and supporting me to be part of a wide variety of outbreaks. In particular, I acknowledge the vaccine preventable diseases team, enteric team, vector borne diseases team and sexually transmitted infections team, who involved me in investigations and invited me to observe relevant IMTs to support me to gain a breadth of experience.

I also thank the CDES leaders, particularly Janet Strachan and Lucinda Franklin, who advocated for my involvement in outbreaks and endeavoured to facilitate opportunities with Local Public Health Units (LPHUs), as outbreak investigations increasingly transitioned to being managed by LPHUs over the course of my MAE.

I acknowledge and thank the Immunisation Unit for involving me in the vaccine CCB investigation. In particular, I thank Rebecca Gang and Megan Beasley, for facilitating this opportunity and working to get me involved in other acute public health incidents.

Finally, I thank all of my supervisors for their support in finding an appropriate outbreak, and in developing the write up of the two components of this chapter.

PART A: PEER REVIEWED PUBLICATION

LESSONS FROM THE RE-EMERGENCE OF IMPORTED
MEASLES CASES FOLLOWING THE COVID-19 PANDEMIC
IN VICTORIA, AUSTRALIA



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Lessons from the re-emergence of imported measles cases following the COVID-19 pandemic in Victoria, Australia

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Lessons from the re-emergence of imported measles cases following the COVID-19 pandemic in Victoria, Australia

Madeleine J Marsland, Janet Strachan, Rebecca F Gang, Miriam O'Hara, Nicole M Hughes, Anna Glynn-Robinson

Abstract

Introduction

Australia was declared to have eliminated endemic measles in 2014; however, imported cases continue to pose a threat of outbreaks. International travel restrictions during the coronavirus disease 2019 (COVID-19) pandemic led to a rapid decline in measles cases. The re-opening of the Australian international border to measles endemic regions returns the threat of outbreaks, which may be further compounded by disruptions in routine vaccinations during the COVID-19 pandemic. We consider lessons learned from the public health response to recent measles cases.

Methods

This case series includes all confirmed measles cases meeting the national case definition reported to the Victorian Government Department of Health (the Department) between 1 January and 31 December 2022. The Department conducted active case finding and contact tracing of all cases in line with national guidelines. Cases were descriptively analysed.

Results

In 2022, six of the seven measles cases reported in Australia occurred in Victoria, all of whom resided in Australia and acquired their infection overseas. Three cases were unlinked, and three formed an epidemiologically-linked household cluster. One case was partially vaccinated, one was not eligible for vaccination, one had unknown vaccination status, and three were unvaccinated, one of whom was under 12 months old but would have been eligible for vaccination prior to travel to endemic regions. None of the cases led to secondary transmission within Australia.

Discussion

Following the COVID-19 pandemic, measles importations have re-commenced in Victoria. Although few measles cases occurred in 2022 and none resulted in onwards transmission, imported measles cases remain complex and require substantial public health follow-up. Delays in case diagnosis and flight contact tracing pose a significant risk for outbreaks of measles. Public health interventions are needed to maintain high vaccination rates, improve contact tracing, and ensure public health authorities and healthcare providers can rapidly identify and respond to imported measles cases.

Keywords: measles; communicable diseases, imported; communicable disease control; epidemiology

Introduction

Measles is a highly contagious viral infection with the potential to cause severe complications including death, though this is uncommon in Australia.^{1,2} The incubation period for measles is 10 days (ranging from 7 to 18 days),³ and has rarely been reported up to 23 days.^{1,4} Measles has one of the highest reproductive numbers for a directly transmitted pathogen, ranging from 12 to 18 in susceptible populations.^{1,2} Humans are the only known reservoir.²

In Australia, two doses of measles-containing vaccine are recommended for all children aged ≥ 12 months, with children aged ≥ 6 months able to receive one dose when travelling to regions with high endemic transmission or outbreaks.⁵ Vaccination against measles is freely available under the National Immunisation Program (NIP), with the two-dose schedule conferring 99% protection.⁵

People can be vulnerable to infection if unvaccinated or partially vaccinated according to Australian standards, or due to inadequate immune response or waning immunity.^{6–8} Individuals born pre-1966 are considered to have natural immunity due to likely infection in childhood, and are not eligible for free vaccination within Victoria, though some may not be immune.^{6–8} Individuals born in the 1970s may also not have natural immunity as a result of reduced measles exposure, and may be susceptible due to single-dose schedules during this period.⁹

The World Health Organization (WHO) declared Australia to have eliminated endemic measles transmission in 2014.¹⁰ Almost all cases now reported in Australia are either imported or related to an imported case.^{7,8} Imported measles has occasionally resulted in tertiary spread of the disease, most recently in 2019,¹¹ demonstrating a continued threat of the re-introduction of measles into Australia if high vaccination coverage levels are not maintained. Globally, measles eradication efforts are ongoing, with cases declining between 2000 and 2016.^{1,12} However,

between 2017 and 2019 a worldwide resurgence of measles occurred, with outbreaks in regions where measles had previously been declared eliminated.^{1,12–14}

The coronavirus disease 2019 (COVID-19) pandemic resulted in Australia closing its international borders in 2020,¹⁵ leading to measles cases rapidly declining. In Victoria, 57 measles cases were reported in 2019, compared to only five in 2020 prior to travel restrictions, and there were no measles cases in Australia in 2021.¹⁶ With the reopening of international borders in February 2022,¹⁵ measles importations have recommenced, with seven measles cases reported nationally in 2022, six of which occurred in Victoria.¹⁷ The risk of outbreaks may be increased due to globally-disrupted vaccinations during the pandemic,^{1,18} although childhood vaccination rates have remained high among most population groups in Victoria.^{1,19}

Imported measles cases can lead to localised outbreaks and ongoing transmission, which may ultimately result in re-establishment of endemic transmission if there are immunity gaps.^{6,8,11,12} We consider lessons learned from the re-emergence of imported measles in Victoria following the COVID-19 pandemic.

Methods

Case series analysis

This case series included all confirmed measles cases reported to the Victorian Government Department of Health (the Department), from 1 January 2022 to 31 December 2022, which met the Australian national notifiable diseases case definition.²¹ Cases were descriptively analysed.

Epidemiological investigation

Measles is an urgent notifiable condition in Victoria, with a statutory requirement that all suspected, probable and confirmed cases are notified to the Department.²²

The Department conducted enhanced surveillance, active case-finding and contact tracing for all confirmed cases in line with the Communicable Diseases Network Australia (CDNA) Measles National Guidelines for Public Health Units (CDNA guideline).³ For each case, interviews were conducted with the case, healthcare provider, and/or next-of-kin as appropriate, to identify all potential contacts and exposure sites. All associated case and contact data were stored in Victoria's Public Health Event Surveillance System (PHESS).

The likely source of acquisition for each case was identified based on the case's risk history including any overseas travel, with the support of genomic testing as appropriate. Cases were considered epidemiologically linked if there was evidence of contact involving plausible transmission,³ and were classified as clustered if there was more than one case within a household group. Cases were considered infectious from one day prior to prodromal onset, until four days after onset of their rash, and were isolated in their home or a healthcare setting from initial suspicion of measles diagnosis until the infectious period was complete. Monitoring of the event concluded two incubation periods (upper limit: 36 days) after the case (or last case in a cluster) was released from isolation.

Vaccination status of cases and of identified contacts was confirmed via the Australian Immunisation Register (AIR), or via records provided by cases and contacts or their next-of-kin. The vaccination status of cases was classified as 'unknown' if the case was unable to provide evidence of prior vaccination, and 'not eligible' if the case was born prior to 1966.

The Department notified all face-to-face contacts (those identified by the case or next-of-kin) of their potential exposure via telephone. Where evidence of measles vaccination was not available, contacts were encouraged to undergo serological testing to confirm their immune status (i.e., immunoglobulin G [IgG] antibodies for measles), and, if applicable, were offered appropriate post-exposure prophylaxis (PEP)

(i.e. measles-containing vaccination within three days, or normal human immunoglobulin within six days of first exposure).^{3,5} Contacts were regularly monitored via text message or telephone call (usually every 2–4 days) until 18 days after last contact with the case. Healthcare facilities conducted contact tracing and coordinated PEP for exposures that occurred on healthcare grounds (e.g. emergency departments or primary healthcare facilities). Chief Health Officer (CHO) alerts were issued where public exposure sites were identified and premises were provided with advice; however, contacts at these sites were not individually followed up.

Where a case travelled on an international flight during the infectious period,³ details of flight contacts were sourced via the National Incident Centre (NIC), based at the Australian Government Department of Health and Aged Care. The NIC provided incoming passenger cards (IPCs) for passengers with a Victorian address, with interstate flight contacts followed up by their respective residential states and territories. The IPCs of Victorian residents were manually transcribed, and all passengers were sent information on their exposure and available PEP via email and/or text message. Exposure sites and international contacts were notified to relevant country National Focal Points by the NIC.

Laboratory investigation

Laboratory testing was conducted at the Victorian Infectious Diseases Reference Laboratory (VIDRL), the national measles reference laboratory for Australia and a WHO measles regional reference laboratory.^{23,24} All cases were confirmed to have measles via polymerase chain reaction (PCR) testing. Genotyping was performed by nucleic acid sequencing with phylogenetic analysis conducted after PCR testing,^{23,24} to support epidemiological investigation.

Ethics

Case investigations were conducted under the *Victorian Public Health and Wellbeing Act 2008* with an ethics waiver from the Australian National University Human Research Ethics Committee (2017/909).

Results

Six confirmed measles cases were reported in Victoria in 2022, all occurring between June and December (Table 1). Three cases were single imported cases, and three cases formed part of an epidemiologically-linked household cluster. All cases acquired their infection overseas. Key findings of the outbreak investigation are reported below.

Case one

Case one presented to a health clinic five days after entering Australia from Europe after receiving notification from a European Health Department of exposure to a confirmed measles case on a flight entering Europe. She reported a four-day history of headache, dry cough, sore neck, and sore eyes and a one-day history of maculopapular rash commencing on her face and progressing to her torso. PCR testing confirmed a measles diagnosis.

Genomic sequencing confirmed the case's strain (genotype B3) was identical to the European case, and matched strains identified in Europe in January and May of 2022. She had a prolonged incubation period of 20 days between contact with the known measles case and onset of the rash. The case had evidence of prior measles-containing vaccination in her country of birth, receiving one dose at six months of age, and a

Table 1: Summary of demographics and epidemiological data for confirmed measles cases in Victoria, 2022

Case designation	Linked	Sex	Age group (years)	Born in Australia	Resides in Australia	Genotype	Source (likely place of acquisition)	Vaccination status	Estimated number of contacts ^a
One	No	Female	30–34	No	Yes	B3	Imported (Europe)	Partially vaccinated	157
Two	No	Female	40–44	No	Yes	D8	Imported (South Asia)	Unknown ^b	54
Three	No	Male	55–59	Yes	Yes	D8	Imported (Southeast Asia)	Not eligible ^c	14
Four	Household cluster	Male	1–4	Yes	Yes	D8	Imported (Middle East)	Not vaccinated	6
Five		Female	5–9	Yes	Yes	D8	Imported (Southeast Asia)	Not vaccinated	
Six		Female	< 1	Yes	Yes	D8	Imported (Southeast Asia)	Not vaccinated ^d	

a Includes close contacts, contacts identified by healthcare facilities, and contacts from public exposure sites where this was estimated.

Excludes flight contacts and contacts from public exposure sites where it was not possible to estimate these numbers.

b Vaccination status was classified as unknown when the case reported having a measles vaccination but was not able to provide evidence.

c Vaccination status was classed as not eligible when the case was born prior to 1966.

d The case was considered not vaccinated as they were ≥ 6 months of age when they travelled to a measles endemic region, and therefore was eligible to receive a recommended measles-containing vaccine.

second dose at 15 months of age. However, as she had received her first dose under the recommended age of 12 months, to be considered fully vaccinated under current Australian guidelines, the case should have received a third dose of measles-containing vaccine.⁵ This case was therefore considered to be partially vaccinated.

The Department identified 38 close contacts, and the health clinic she attended identified seven contacts who were offered PEP. A CHO alert was issued identifying public exposure sites. The case had travelled extensively across Victoria, as well as into New South Wales, requiring collaboration with interstate counterparts. Approximately 112 individuals were estimated to have had contact with the case at public exposure sites. The Department notified people who were on the flight with the case entering Australia. No further cases were identified.

Case two

Case two presented to a healthcare facility four days after entering Australia from South Asia with a five-day history of cough, coryza and conjunctivitis, and a two-day history of a maculopapular blanching painful rash. She was not assessed for measles at the time and re-presented to the hospital two days later due to worsening symptoms. Measles diagnosis was confirmed via PCR.

The case spent her entire incubation period in South Asia, and whilst a particular source could not be identified, genotyping confirmed the likely origin of the strain (genotype D8) was exposure in South Asia, with the last detection of this strain occurring in 2018. The Department identified ten close contacts and notified flight contacts; however, PEP was not offered due to the delayed diagnosis of this case beyond six days from the time of the flight. Healthcare clinics identified and provided advice to a further 44 contacts. Several public exposure sites were identified, including large shopping centres, and a CHO alert was issued. The number of contacts at these locations was unable to be estimated. No further cases were identified.

Case three

Case three was admitted to a hospital ten days after entering Australia from Southeast Asia. He had an eight-day history of cough, coryza and ongoing fever, and had been diagnosed with COVID-19 from a Rapid Antigen Test (RAT) on the first day of his illness. He also had a two-day history of cranio-caudal exanthem rash. PCR testing confirmed a measles diagnosis. The case was considered not eligible for vaccination as he was born prior to 1966.

This is the first known case of measles and COVID-19 co-infection in Australia. Given the overlap of symptoms, the infectious period for measles was based on the emergence of the rash,³ and flight contact tracing was subsequently not required. The Department identified 14 close contacts; however, PEP was not offered due to delayed diagnosis beyond six days from time of exposure. There were no public exposure sites associated with this case as he had been isolating due to COVID-19. No further cases were identified.

Household cluster: cases four, five and six

Three young siblings presented to a health clinic one day after returning to Australia from Southeast Asia. All the children were unvaccinated. The youngest child was aged < 12 months but had been ≥ 6 months old at the time of travelling to a measles endemic region.

Case four had experienced a measles-like illness in Southeast Asia after travelling from the Middle East, with a five-day history of runny nose and sore throat followed by the development of a rash. The family had sought care in Southeast Asia and been advised the child probably had measles, although laboratory testing was inconclusive. The family remained in isolation until four days after symptom resolution before returning to Australia.

The family presented in Australia after case five and six experienced subjective fevers. All three cases tested PCR-positive for measles. Case four was considered the likely index case

for cases five and six. Based on the incubation period, the index case likely acquired measles in the Middle East, with onwards transmission to their siblings within Southeast Asia. All cases were classified as imported.

The Department identified six close contacts, and eligible contacts were offered PEP. There were no healthcare contacts associated with these cases. Flight contacts were notified of exposure and a CHO alert was issued, given the airport was a public exposure site. No further cases were identified.

Discussion

There remains significant complexity in rapidly identifying and responding to measles cases, even in a low-incidence environment. Australia experienced a reprieve from measles incursions during the COVID-19 pandemic. However, there may now be an increased risk of resurgence.¹ Within this context ongoing prevention strategies, high immunisation coverage and strong surveillance systems are required to prevent outbreaks of measles within Australia.^{6,8,11,12}

There were fewer measles cases reported in Victoria in 2022 compared with the years before the pandemic,¹⁶ and no onwards transmission was identified within Australia. This may be associated with high levels of immunity due to ongoing high vaccination coverage in the community.^{5,25} Four cases (cases three to six) also isolated themselves during their infectious period due to COVID-19 illness or prior awareness of likely measles infection and possible spread. Community health behaviours, such as mask wearing within healthcare clinics, may have also reduced the risk of transmission. There is no guarantee future cases will comply with public health measures, noting people are infectious before the onset of rash, and health literacy is generally an underestimated global health problem.^{26–28} In early 2023, measles cases have been detected in other Australian states and territories,²⁹ so it is timely for public health agencies to be aware of the ongoing risk of outbreaks.

Several cases experienced delays in diagnosis. This can occur due to delays in people presenting with illness, or due to delays in testing, with samples from primary laboratories requiring transport to and confirmation by reference laboratories. Notably, case two attended a hospital twice before being diagnosed. Measles is often missed in clinical settings as many Victorian medical practitioners have little first-hand experience of measles.³⁰ Delayed diagnosis can hinder contact tracing efforts, leading to contacts missing out on PEP.³⁰ Furthermore, transmission can occur within healthcare settings, particularly if cases are not rapidly identified and isolated.³¹ Healthcare workers must be constantly vigilant for potential measles cases, with CHO advisories for doctors warning of travel-related infectious diseases and alerts associated with imported cases providing opportunities for regular reminders.^{30,31} The way people access and consume news is changing, shifting from traditional media (e.g. newspapers) to social media, so CHO alerts which typically use traditional media may no longer be the best way of reaching all populations and social media should be used to disseminate alerts.

Most measles cases that occur within Australia are unvaccinated,⁷ with only one case in this series having evidence of immunisation. The partially vaccinated case had a prolonged incubation period, suggesting a modified measles infection.^{32,33} Attenuated measles presentations are increasing in Victoria, and can be challenging to diagnose, demonstrating further the benefit of having two valid measles-containing vaccinations administered, and the need for clinicians to be alert for modified measles infections.^{32,33} Several factors are thought to increase the risk of individuals being unvaccinated or having incomplete vaccinations; these include being from a larger family not using formal childcare services, being from a single parent household, poor social supports, being overseas-born, receiving immunisations from general practitioners, and being a late starter to immunisation.^{25,34} Two adult cases (one and two) and the parents of the three children (cases four to six) were overseas-born. Within

the household cluster, all children were unvaccinated despite recommendations and readily available measles vaccination in Australia. Preventing measles transmission should focus on maintaining high vaccination rates across Australia, including in populations who may have missed routine childhood vaccinations, such as migrant populations, and who may require additional education and support to be aware of available immunisation services.⁷

Flight contact tracing was required for five of six cases in this series. Measles cases on flights pose a heightened risk of transmission, with cases potentially able to widely transmit within a confined space, and contact tracing often ineffective, incomplete and delayed, as passenger lists and IPCs can be difficult to access.^{35–37} Transmission can also occur within airport settings during the pre-flight or post-flight period.^{37,38} Flight contact tracing was a critical control measure during the early months of the COVID-19 pandemic,³⁹ leading to the introduction of digital passenger declarations to support large-scale contact tracing.⁴⁰ However, this pathway in Australia is no longer available. Among the six cases in this series, there were often delays in acquiring and manually transcribing IPCs, as they came in batches over days and weeks. Timeliness is critical for measles public health actions, and for some cases the window to offer PEP for flight contacts expired.³⁸ Delays in contact tracing can also lead to contacts being missed and delayed diagnosis of secondary cases, potentially contributing to onwards transmission. Further work is needed to improve processes to support flight contact tracing, including digitisation of passenger cards, and working with airlines and airports to facilitate more timely access to flight manifests.

This case series was limited by the small number of cases that occurred in 2022, and may not be representative of cases that occur in the future. The findings and lessons may also not be applicable to all Australian states and territories, as the public health systems, infrastructure and resources vary, affecting jurisdictions' ability to implement public health actions. None of

the cases led to transmission within Australia, so it was not possible to test the public health response to secondary cases or to consider the impact of the COVID-19 pandemic on local transmission of measles.

Despite these limitations, this case series provides a useful overview of lessons learned from responding to the first measles cases to occur in Victoria following a pause in cases during the COVID-19 pandemic. Measles contact tracing is resource-intensive, with one international study noting that the response cost for even a single case that does not result in transmission can be as high as \$142,000 USD.⁴¹ Public health follow up requires considerable time and effort,³⁸ highly skilled and trained personnel, and close collaboration with local, interstate, national and international health agencies. It is timely to consider the lessons from the re-emergence of imported measles and opportunities to improve Victoria's response to prevent potential outbreaks in the future. This case series is also of use to other Australian states and territories where measles is also re-emerging after the COVID-19 pandemic.

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PART B: INVESTIGATION OF A VACCINE COLD CHAIN
BREACH IN A HEALTH FACILITY IN VICTORIA, AUSTRALIA

ABSTRACT

Introduction

A vaccine cold chain breach (CCB) occurs when a temperature-sensitive vaccine is exposed to temperatures outside of the recommended range, leading to the vaccine potentially losing potency. We report the public health response to a vaccine CCB that occurred in a Victorian health facility in 2023.

Methods

The health facility conducted a self-audit to identify the underlying causes of the CCB and ensure compliance with national vaccine storage guidelines. Data were extracted from the health facility's clinical management software and compared with the Australian Immunisation Register, to identify the patients who had received vaccines impacted by the CCB. Where appropriate, patients were offered re-vaccination, in line with expert advice. The results of the self-audit and re-vaccination program are descriptively analysed and reported.

Results

The investigation determined the cause of the CCB was human error during maintenance of the purpose-built vaccine refrigerator, impacting the continuous temperature monitoring. In total, 64 impacted patients were identified, who had received 95 vaccine doses. Of these, 58 patients were recommended to be re-vaccinated with at least one vaccine (total 72 vaccine doses) with 42 patients (53 vaccine doses) receiving re-vaccinations. Of those who did not receive re-vaccinations, four declined re-vaccination, eight were lost to follow-up and four patients either did not attend their appointment for revaccination, or were undecided about being revaccinated.

Discussion

Further work is required to prevent vaccine CCBs in Victoria, and to rapidly identify and respond if they occur. Particular challenges associated with responding to this CCB included the need to work with multi-agency teams, and issues with data recorded in the Australian Immunisation Register. CCBs have the potential to leave at-risk populations unprotected from vaccine preventable diseases.

INTRODUCTION

As Australia has progressively introduced effective vaccines onto the National Immunisation Program (NIP), the burden of vaccine preventable diseases (VPDs) has declined [1]. At a population level, there is a need to maintain high vaccination coverage to maximise protection, particularly in the wake of the COVID-19 pandemic [2].

In order for vaccines to be effective in their intended populations, well-functioning vaccine cold chain processes are required [3]. The Australian Government Department of Health and Aged Care publishes guidance on vaccine storage for immunisation service providers (national vaccine storage guidelines) [4]. A cold chain breach (CCB) occurs when a temperature-sensitive vaccine is exposed to temperatures outside of the recommended range (2°C to 8°C), excluding fluctuations up to 12°C lasting less than 15 minutes, or is exposed to light as the vaccine is removed from the packet [4-6]. Vaccine CCBs can occur at any stage in the cold chain, including during storage, shipment, transport or outreach [3]. The Victorian Department of Health (DH) publishes additional guidance on vaccine storage including the steps to take for reporting a CCB in Victoria [7].

CCBs can lead to vaccines losing potency, potentially placing individuals at a higher risk of infection with a VPD, and contribute to vaccine wastage which is estimated to cost Australia as much as \$16 million annually [3, 8]. Globally, there is evidence that CCBs are common [3, 9]. Large outbreaks of VPDs such as measles, hepatitis B and pertussis have been reported in both high income and low income countries that have experienced high rates of CCBs [3]. Globally in recent years, a range of measures, such as increased staff education, supervision and technical guidance, have improved cold chain monitoring [3, 9].

In 2023, DH received notification of a CCB that occurred at a health facility in Victoria. We report the outcomes of the CCB investigation and lessons learned, to inform the management of future CCBs and prevention activities.

METHODS

Investigation

A temporary freeze event occurred in the health facility's Purpose Built Vaccine Fridge (PBVF), with a recorded minimum temperature of -3.1°C. The health facility detected the event eight days after it occurred, and notified DH the following day. All vaccines stored in the fridge within this 9-day period were considered to be impacted by the CCB.

An Incident Management Team (IMT) was established with representatives from DH (Immunisation Unit, Media Unit), the health facility, and the central reporting body for adverse events after immunisation in Victoria, Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC). The IMT conducted the investigation in 2023 and provided advice on re-vaccination (see below).

DH suspended the health facility's government-funded vaccine account while a self-audit was conducted to ensure the health facility was compliant with the national vaccine storage guidelines. DH provided the health facility with guidance on self-auditing, to identify the underlying cause of the CCB. Results of the self-audit are described (Appendix A). Temperature-sensitive vaccines stored in the PBVF that had not been used were discarded in line with internal guidance regarding freeze breaches $\leq 0^{\circ}\text{C}$.

Re-vaccination

An 'impacted patient' was defined as a person who received a vaccine at the health facility during the 9 days impacted by the CCB. The health facility extracted a computer-generated report from their clinical management software of immunisations provided during this period. Medicare numbers were utilised to link this data to the Australian Immunisation Register (AIR), and records for vaccine doses given to the impacted patients were extracted.

A line list of impacted patients and relevant vaccine doses was prepared. SAEFVIC provided expert clinical advice on the affected vaccines and the impacted patients who should be re-vaccinated. The health facility distributed letters and frequently asked questions (Appendix B) to impacted patients, or their parent/guardian where relevant, using their clinical management software.

Impacted patients who were identified as requiring re-vaccination were encouraged to be re-vaccinated at least four weeks following their initial vaccination. The health facility recorded re-vaccinations and provided completed documentation to DH. For the purposes of this investigation, data on re-vaccinations were extracted three months following the CCB, and it is possible that some additional follow-up and re-vaccination may have occurred after this time. In addition, impacted patients were able to choose to be re-vaccinated at another health clinic, which may have led to an undercount in the patients choosing to be re-vaccinated. AIR records were checked for all impacted patients to try to identify individuals who may have received re-vaccinations elsewhere. Results of impacted patients were descriptively analysed using Microsoft Excel (2022).

Ethics

The CCB investigation received an ethics waiver under the Australian National University Human Research Ethics Committee Protocol 2017/909.

RESULTS

Investigation

The cause of the CCB was determined to be human error after maintenance on the PBVF impacted the continuous temperature monitoring of the PBVF where the vaccines were stored. A service repair person had loosened the door during servicing, which had resulted in the fan switch being disabled leading to the fan being switched off during the CCB. There was also insufficient temperature monitoring resulting in delayed awareness of the breach (Appendix A). The service repair person re-assessed the PBVF during the investigation and noticed some high temperatures unrelated to the CCB, which were resolved with replacement parts. The self-audit also identified a range of other high-risk concerns (Appendix A) requiring action to improve the cold chain management at the health facility. DH provided advice on actions to take as part of a cold chain management systems improvement plan.

The health facility completed all required actions and relevant staff members completed the DH Cold Chain Management eLearning modules [10]. DH subsequently reactivated the health facility's government supplied vaccine account following the completion of the activities, to enable the re-vaccination program to commence.

Re-vaccination

A total of 64 impacted patients were identified (Figure 1, Table 1). As at three months following the CCB, 56 (88%) impacted patients had been successfully contacted by the health facility, with eight patients (8 recommended vaccine doses) considered lost to follow-up (Figure 1).

The median age of impacted patients was 34.5 years (range 6 weeks to 79 years), with 15 (23%) being children aged <5 years. Impacted patients received a combined total of 95 vaccine doses (median 1 dose, range of 1 to 4 doses), with children aged <5 years receiving most of these doses (42 doses combined, median of 3 doses, range 1 to 4 doses).

In line with SAEFVIC's advice, 58 of 64 (91%) impacted patients were recommended to receive re-vaccinations, with the remaining six impacted patients not recommended due to other medical factors including pregnancy. Of the 95 impacted vaccine doses, 72 doses were recommended to be administered as re-vaccinations and 23 doses not recommended to be

administered for re-vaccination due to vaccine type (i.e. no re-vaccination required) or other patient medical factors (Table 1).

Of the 58 impacted patients recommended for re-vaccination, 42 patients received re-vaccinations (53 doses) within the 3-month analysis period, with 39 receiving re-vaccinations at the health facility, and three receiving re-vaccinations elsewhere (confirmed using the AIR) (Figure 1).

Of the remaining 19 vaccine doses recommended to be re-administered, but were not: eight doses were associated with eight impacted patients lost to follow-up; four doses were associated with four impacted patients who declined re-vaccination; five doses were associated with three impacted patients who agreed to be re-vaccinated but did not attend their appointments; and two doses were associated with one impacted patient who was undecided about proceeding with re-vaccination.

Figure 1: Summary of re-vaccination outcomes for impacted patients

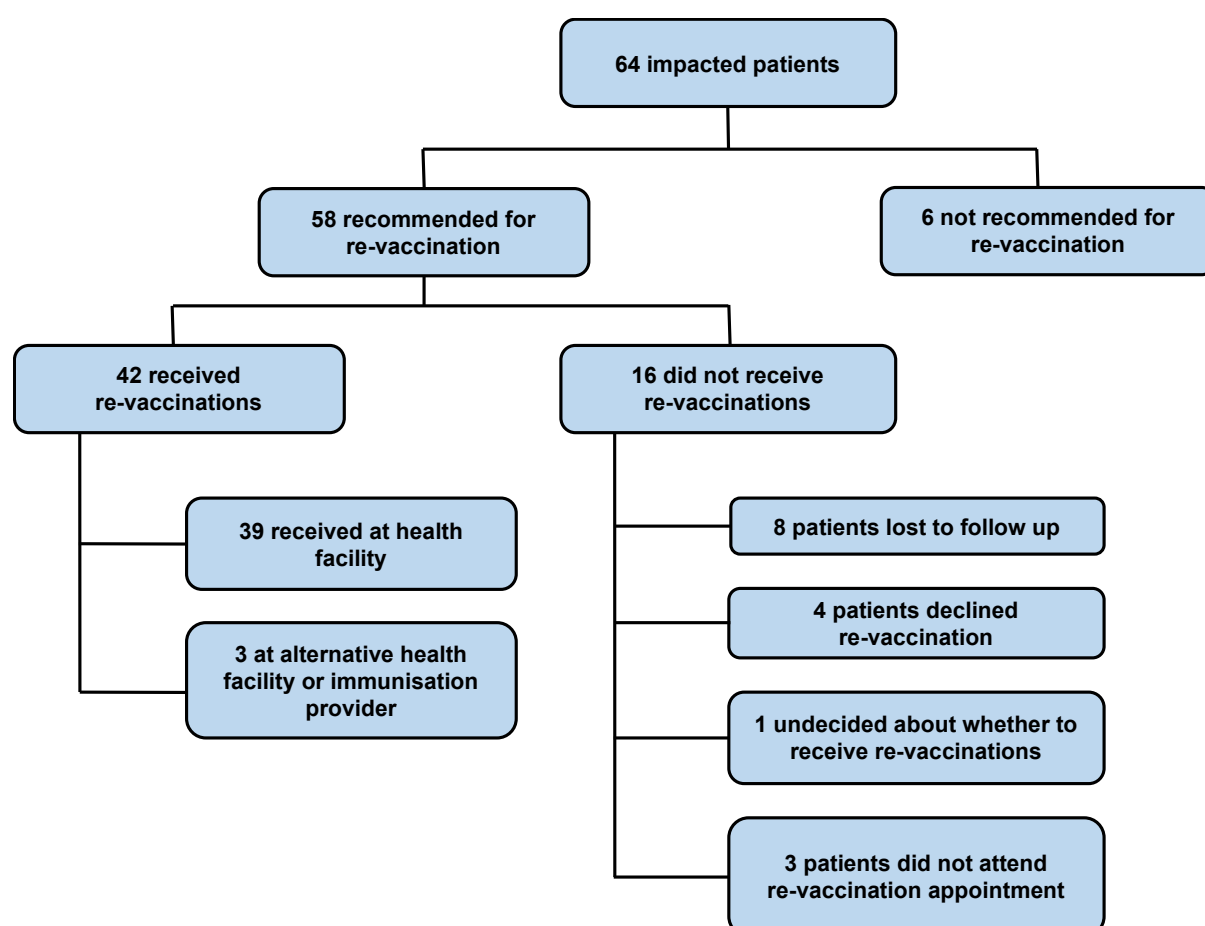


Table 1: Summary of impacted patients and doses received

Age group (years)	Total impacted patients	Total who received re-vaccinations*	Vaccine given to prevent	Doses eligible for re-vaccination	Doses re-vaccinated
<5	15	12	<i>Haemophilus influenzae</i> type b	1	1
			Meningococcal serogroup B	10	7
			Meningococcal serogroups ACWY	3	2
			Diphtheria, Tetanus, Pertussis	1	1
			Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis	7	6
			Diphtheria, Tetanus, Pertussis, Poliomyelitis	1	1
			Influenza	5	5
5 – 19	11	9	Diphtheria, Tetanus, Pertussis	1	0
			Human Papillomavirus	1	0
			Influenza	10	9
>19	38	21	Influenza	32	21
Total	64	42		72	53

* At least one recommended re-vaccination dose received

DISCUSSION

This event demonstrates the ongoing risk of CCBs and the need to optimise the public health follow-up when CCBs occur to ensure people receive potent vaccines.

Research suggests further work is required to prevent CCBs in the future [3, 4, 8, 11]. Recent CCBs in Victoria have been associated with untrained staff, the incorrect use of vaccine storage equipment, and inadequate vaccine storage equipment [11]. This CCB was primarily associated with human error during maintenance of the PBVF. However, a number of additional concerns were identified as part of the self-audit including a need to improve temperature monitoring and data logging, staff training and signage around the PBVF (Appendix A). This demonstrates the need for continual monitoring of vaccine storage arrangements and procedures to ensure good vaccine storage practices within health clinics,

and the rapid identification of CCBs if they occur. New requirements are being introduced to support prevention of CCBs, and since August 2023, Victorian health clinics are required to complete Cold Chain Management eLearning modules in order to continue to have access to government-funded vaccines [5].

Although the majority of impacted patients that were recommended for re-vaccination had vaccines re-administered, some (16/58, 28%) declined re-vaccinations, were lost to follow-up or did not attend scheduled re-vaccinations. CCBs pose a direct risk to those impacted, as these individuals are at potential risk from being infected with VPDs. There are also indirect risks as CCBs may undermine trust in vaccinations, both for those affected and those who become aware of incidents. Whilst routine vaccination coverage has remained high in recent years, certain populations including children and Aboriginal and Torres Strait Islanders have seen a slight reduction during the COVID-19 pandemic [12, 13]. There is an ongoing need to improve access to vaccination and vaccination rates within these groups.

There were several challenges in responding to this CCB. Mandatory reporting to the AIR commenced in July 2021 [14], so all NIP vaccinations given during the CCB should have been recorded. However, there were initially discrepancies identified between the clinical management software-generated report and data extracted from the AIR. When comparing the initial line-lists, there were 26 individuals identified in the extract from the AIR that were not listed in the data extract from the health facility, and four individuals listed in the extract from the health facility that could not be identified in AIR. These discrepancies were rectified by the health facility and were attributed to influenza vaccinations that had not been uploaded due to human error. This demonstrates the importance of improving provider reporting to AIR, but also highlights the need to maintain and regularly update local clinic records.

There were additional issues with the AIR data, including errors in the information recorded by the health facility such as the use of outdated vaccine codes. Under-reporting to the AIR and the inability to document and report on risk criteria have been long-standing issues, impacting the reliability and accuracy of vaccination data [14-16]. It is also notable that whilst re-vaccinations are able to be recorded in AIR, there is currently no mechanism in place to record doses as being re-vaccinations, or to identify which doses had been impacted but patients were not re-vaccinated. This may have implications for future reporting if these patients go on to develop VPDs. Services Australia may wish to consider amendments to support the recording of vaccinations associated with CCBs in the future.

There are some useful lessons to consider in the management of future CCBs. The response to this CCB required a multi-agency IMT to rapidly come together with representatives from the health facility, and establish systems to support the secure sharing of information. It is important that steps taken to achieve this are well documented to assist in preparation for responding to CCBs that arise in the future. The self-audit undertaken by the health facility also identified a number of issues that were occurring prior to the CCB, and it is worth highlighting that these may not have been detected without the CCB occurring. The national vaccine storage guidelines recommend that self-audits are performed at least every 12 months as a critical preventive action [4]. CCBs are often avoidable and have the potential to lead to community members being unprotected against VPDs. Further work is needed to raise awareness about the risk associated with CCBs and to support health clinics to improve their vaccine storage practices.

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APPENDIX A: COLD CHAIN MANAGEMENT SELF-AUDIT MAY 2023

Action required – [REDACTED]

High risk concerns identified		Action required
1. Staff training	Not all staff have received orientation and/or annual update on vaccine management	Orientate all new staff and update existing staff on vaccine management.
2. Monitoring equipment	Data logger recording read intervals in 20-minute increments instead of 5 minute read intervals	Recalibrate data logger settings to record 5 minutely read intervals. See 5.6 Monitoring and recording refrigerator temperatures .
	No portable data logger Back to base system in built to refrigerator – connectivity during power outage?	Purchase additional portable data loggers for continuous temperature monitoring
	Insufficient number of portable minimum/maximum thermometers	Purchase portable minimum/maximum thermometers for use in emergency storage, transporting vaccines, or outreach clinics.
3. Vaccine refrigerator	No sign at power outlet for vaccine refrigerator 'Do not turn off or disconnect this refrigerator'	Place sticker at power outlet 'Do not turn off or disconnect this refrigerator'. See National Vaccine Storage Guidelines 'Strive for 5' — sticker 1
	No map or guide located on outside refrigerator door showing where vaccines are stored	Place map or guide on the outside of refrigerator door showing where vaccines are stored inside refrigerator
4. Monitoring equipment	Minimum/maximum thermometer battery change	Change the thermometer battery at least every 6 to 12 months or as indicated by the manufacturer.
	Accuracy check of thermometer (aka: slush test) Placement of minimum/maximum thermometer probe	Check the accuracy of the thermometer at least every 12 months (see Section 4.4 'How to check the accuracy of a thermometer ['slush test']'). Place the end of the sensor probe in an empty vaccine box inside the refrigerator to ensure that the probe is measuring the temperature under the same conditions as for the vaccines
	Data logger battery change	Change the data logger battery at least every 6 to 12 months or as indicated by the manufacturer.

APPENDIX B: FREQUENTLY ASKED QUESTIONS FOR IMPACTED PATIENTS

[REDACTED]

Frequently asked questions about a vaccine cold chain breach

What has happened?

The [REDACTED] has identified a temperature breach in a fridge used to store vaccines. This means the vaccines had not been kept at the right temperature and may not work effectively. A full review is being undertaken to avoid any future incidents.

What vaccines were affected?

The vaccine brand/s administered to you and affected by the temperature breach are documented in your letter.

Who does this affect?

People who received the affected vaccines between [REDACTED] 2023 to [REDACTED] 2023.

What does this mean for me?

If you received a vaccine between [REDACTED] 2023 to [REDACTED] 2023 then you may need to be revaccinated to ensure you have best protection against the disease you were vaccinated for.

You can arrange to be revaccinated at the [REDACTED], a local GP, or a community immunisation provider. However, if your health situation has changed you should discuss the revaccination with your GP first.

Will the affected vaccine do any harm?

No. The vaccines that were stored and administered outside the recommended temperature range will not cause harm. The incorrect storage of the vaccine means it may not provide best protection against the disease it was given for. Therefore, you may be recommended to be revaccinated.

Are there health risks in being given the vaccines again?

No. There are no increased health risks from receiving an additional dose of vaccine. All vaccines can cause some redness, swelling and pain at the injection site and this may occur after revaccination.

Should I bring the record of the immunisation with me?

You can bring your immunisation record with you to the revaccination appointment if you would like to. After your revaccination appointment, the Australian Immunisation Register will be updated with the valid vaccine dose. If you choose to visit a different vaccination provider for revaccination, your record on the Australian Immunisation Register will be updated regardless of where you receive revaccination.

Can I access my immunisation records?

Yes. If you are eligible for Medicare, you can access your immunisation history statements online through myGov - <https://my.gov.au>. Records are available via the Medicare or My Health Record portal. If you don't have a myGov or Medicare online account, you will need to set them up. You can also request an immunisation history statement to be posted (allow 14 days for delivery) by calling the Australian Immunisation Register on 1800 653 809.

If you are not eligible for Medicare or cannot use Medicare online, you can ask your vaccination provider to provide you with a printed record of the vaccinations you received on the day.

Will I incur any cost for revaccination?

Vaccinations are freely available through the [REDACTED]. If you choose to have the revaccination with another GP, there may be an out-of-pocket cost for administering the vaccine. The vaccines themselves are free.

What if I am due for a COVID-19 vaccine?

The vaccines recommended for revaccination can all be given at any time, before or after the COVID-19 vaccine.

What if I currently am unwell with COVID-19 or have recently recovered from COVID-19 infection?

If you are acutely unwell (such as with a fever or respiratory illness), vaccination should be deferred until you have recovered.

People who have previously been infected with COVID-19 can receive other (non-COVID) vaccines without any minimum interval between COVID-19 and other vaccines. The vaccines recommended for revaccination can all be given at any time, before or after the COVID-19 vaccine.

Who can I talk to if I have further questions about revaccination?

Further advice can be obtained by contacting the [REDACTED]:

telephone [REDACTED]

email [REDACTED]

Alternatively, you can obtain further advice when booking your appointment with the [REDACTED] or another health service.

If you would like to seek expert vaccine advice or a second opinion, contact the Victorian vaccine safety service (SAEFVIC). Please call 1300 882 924 and select option 1.

I experienced an adverse event after my vaccine. Who should I speak to about this?

Adverse events following immunisation in Victoria should be reported to SAEFVIC, the vaccine safety service in Victoria. You or your doctor can make this report online at the following website: <https://www.safevac.org.au/Home/Info/VIC>

If you are concerned about being revaccinated, the staff at SAEFVIC can help provide you with advice and, if needed, can facilitate a referral to an Immunisation specialist, so you can have an individualised consultation.

To receive this document in another format, email the [Immunisation Unit](mailto:immunisation@health.vic.gov.au) <immunisation@health.vic.gov.au>.

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CHAPTER VI

TEACHING EXPERIENCE

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PREFACE

This chapter outlines my teaching experiences during the MAE program and how I met the two associated MAE competencies.

I firstly outline my experience delivering peer-teaching to first year MAE Scholars. The topic for this presentation was *age standardisation* and I delivered this session with two other MAE scholars, Zoe Baldwin and Virginia DeCourcy.

I then describe my experience delivering peer-teaching through a Lessons from the Field (LFF) activity. My LFF topic was *responding to an outbreak of a new or emerging threat*. I developed this teaching exercise and delivered an associated tutorial based on my experiences working in COVID-19, Japanese encephalitis and mpox.

TEACHING THE MAE 2023 COHORT

Background

My MAE cohort was split into small groups (2 – 3 students) to deliver teaching to first year MAE scholars during their first course block. Each group was assigned a topic from the existing MAE curriculum. I was assigned to a group with my fellow MAE scholars Zoe Baldwin and Virginia DeCourcy to teach a session on age standardisation.

We were provided with the teaching material and exercise on age standardisation taught in previous years. We were given an opportunity to update and refine the material to support our teaching session, and then delivered the session in February 2023.

We divided the session into three main components and each led part of the session:

- Zoe Baldwin – introduction, overview of age standardisation, evaluation
- Maddy Marsland – direct age standardisation and exercise
- Virginia DeCourcy – indirect age standardisation and exercise

When we were not actively leading the session, we provided a supporting role being available for questions and moving around the classroom during the exercises to provide assistance to students who were struggling with either the concepts or using Excel.

Lessons learned

In prior years this competency was fulfilled by the MAE cohort conducting short independent teaching sessions which they designed based on what they felt would be beneficial to the first-year cohort. Given the size of my MAE cohort there was a need to shift to a new format where we were in groups and were assigned to a topic. I was initially disappointed by this, as I had been looking forward to being able to design a session from scratch. However, there were a few key benefits and lessons learned that I gained from this experience:

- It was valuable to consider the different views and experiences my group had about age standardisation and how it could best be taught, including how to ensure we were able to cover the essential material for students who had little experience in data analysis and Excel, but were also able to engage and challenge students who were familiar with this topic.
- It was useful understanding the challenges of using material developed by others in teaching. This is something I have often seen in my university experience – lecturers inheriting material initially designed by others. This session made me appreciate both

the benefits and difficulties in adapting material when it's not always clear how it was intended to be delivered.

Acknowledgements

I would firstly like to thank and acknowledge Zoe Baldwin and Virginia DeCourcy, my co-presenters for this session. It was great being able to work closely with them to bring this together. I would also like to thank Anna Glynn-Robinson and Emma Field, our mentors from the MAE program for being available to answer questions and providing advice. Finally, I thank the first year MAE cohort for being a supportive audience.

Teaching session (slides)

Australian National University

Direct Standardisation

- Aiming to calculate the weighted average rate of the age-specific rates (standardised rate)
 - The standardised rate can be compared to other populations that have been standardized in the same way
 - i.e. must use the same standard population

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Maddy

Australian National University

Process of direct standardisation

- Calculate observed stratum-specific rates of disease/death in study population
- Apply these rates to a standard population
- Compare standardised rates

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Process of direct standardisation

Age groups	Number of deaths	Study population	Study population mortality rate	Australian standard population	Study population expected deaths
0-4	51	27821	0.00183	1,282,357	2,351
5-9	7	27451	0.00025	1,351,664	345
10-14	7	24893	0.00028	1,353,177	381
15-19	11	19350	0.00057	1,352,745	769
20-24	14	16514	0.00085	1,392,412	1,104
25-29	19	15348	0.00124	1,407,081	1,742
30-34	25	16157	0.00155	1,466,615	2,269
35-39	38	13646	0.00278	1,492,204	4,155
40-44	51	11643	0.00438	1,479,257	6,480
45-49	61	9189	0.00664	1,358,594	9,019
50-54	64	7295	0.00877	1,300,777	11,412
55-59	68	5066	0.01342	1,008,799	13,641
60-64	76	3350	0.02269	822,024	18,649
65-69	80	2398	0.03336	682,513	22,769
70-74	73	1635	0.04465	638,380	28,503
75+	173	2169	0.07976	1,114,641	88,904
Total	818	203925	0.00401	19,413,240	212,392

Direct standardised rate per 1000 population = $212,392 / 19,413,240 \times 1000 = 10.9$

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Maddy

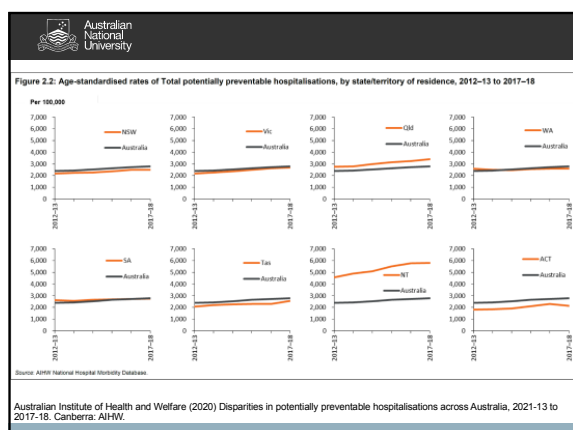
Australian National University

Examples

- Some examples of how two populations with standardised rates might be presented...

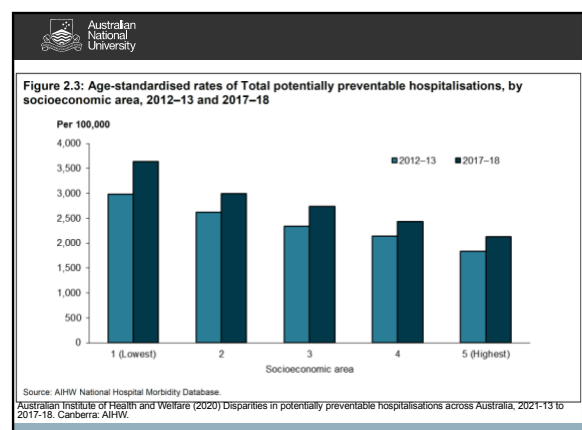
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Maddy



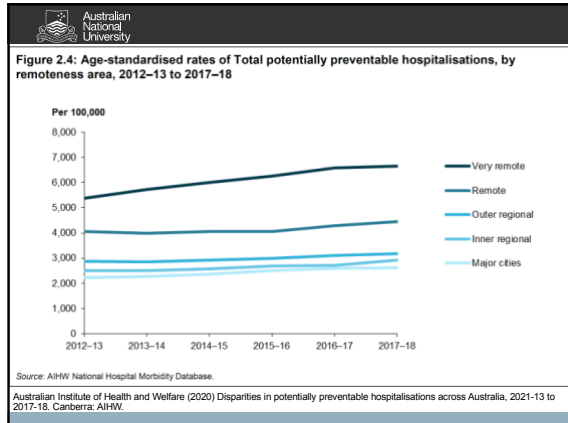
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Exercise

- In this scenario you are a newly employed epidemiologist in Queensland and have been asked to review all cause mortality in females, looking specifically at Indigenous vs non-Indigenous rates for the time period 2002–2004

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Activity 1: Crude mortality rate

STEPS TO FOLLOW

1. Open the excel tab titled 'Crude rates'
2. For the Indigenous observed crude death rate, in cell C2 type the formula $(A2/B2) \times 1000$
3. Calculate the non-Indigenous observed crude rate $(D2/E2) \times 1000$
4. Calculate the rate ratio by dividing the Indigenous by non-Indigenous rate $(C2/F2)$

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Australian National University

Activity 2: Age-specific rates

STEPS TO FOLLOW

1. Open the excel tab titled 'Age-specific rates'
2. For the Indigenous female mortality rate in the 0–4 age group, in cell D3 type the formula $(B3/C3) \times 1000$ and fill down
3. Calculate the non-Indigenous female mortality rate

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Maddy

Australian National University

Activity 3: Direct age standardisation

STEPS TO FOLLOW

1. Open the excel tab titled 'Direct age standardisation'
2. Calculate the female mortality rate for each age group for Indigenous and non-Indigenous females (do not convert to rate per 1000)
 - In cell D3 = $B3/C3$, copy down
 - In cell G3 = $E3/F3$, copy down
3. Calculate the expected notifications (age-specific rate x Australian population) for Indigenous and non-Indigenous
 - In cell I3 = $D3 \times H3$, copy down
 - In cell J3 = $G3 \times H3$, copy down
4. Sum expected notifications
 - In cell I19 = $SUM(I3:I18)$
 - In cell J19 = $SUM(J3:J18)$

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Maddy

Australian National University

Activity 3: Direct age standardisation

STEPS TO FOLLOW

5. Calculate the standardised mortality rate for Indigenous and non-Indigenous females:

Remember: Direct standardised rate per 1000 population = $\frac{\text{sum expected notifications}}{\text{Australian population}} \times 1000$

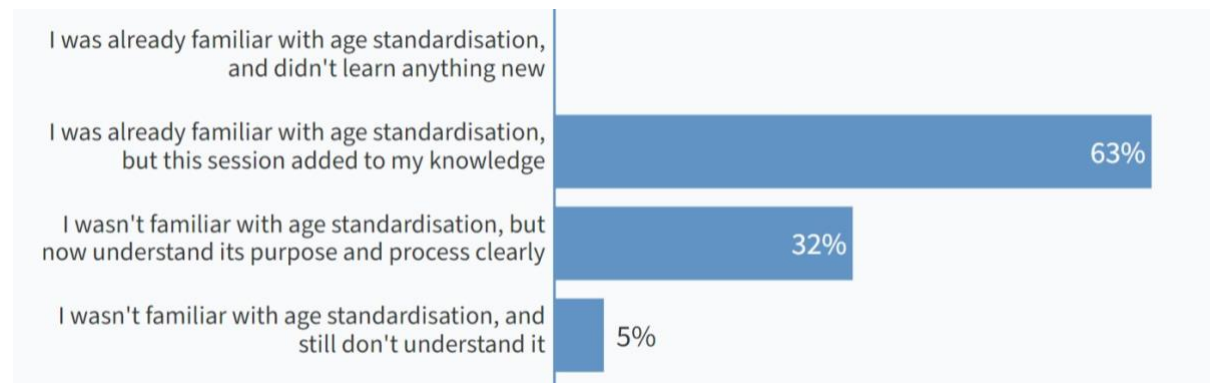
 - In cell F21 = $I19/H19 \times 1000$
 - In cell F22 = $J19/H19 \times 1000$
6. Calculate the Indigenous to non-Indigenous standardised mortality rate ratio (Indigenous standardised rate / non-Indigenous standardised rate)
 - In cell F23 = $F21/F22$

30

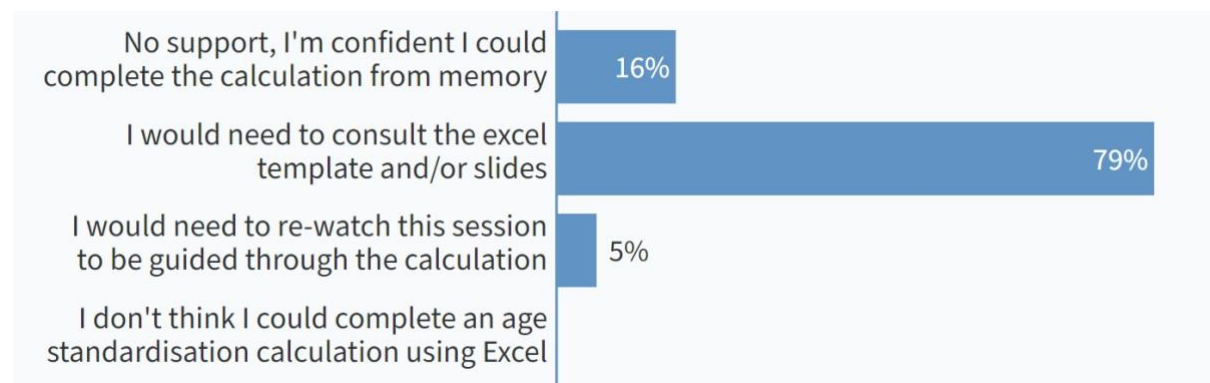
Maddy

Evaluation

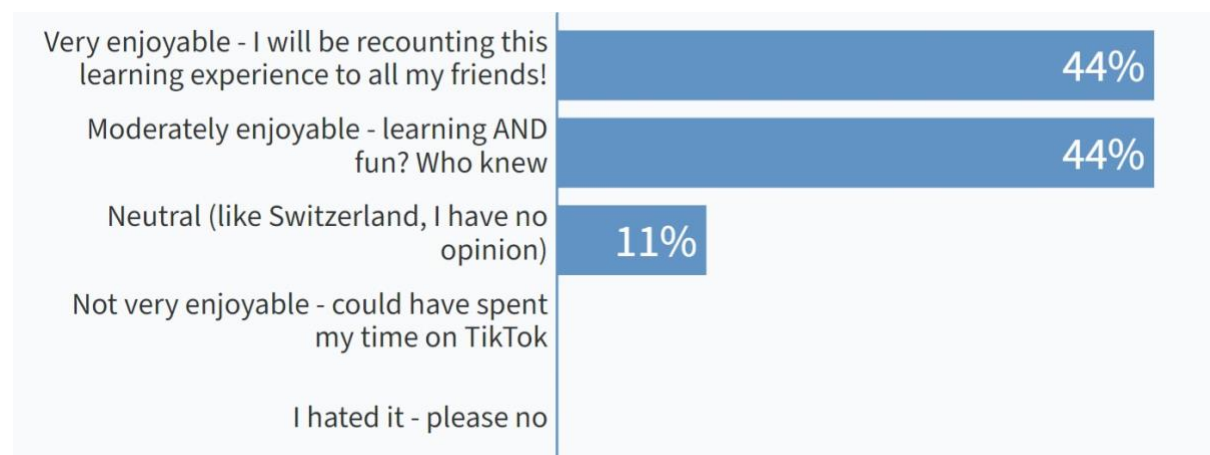
How would you describe your knowledge of age standardisation following this session?



After this session, what support would you need to do an age standardisation calculation in Excel?



How enjoyable was this session for you?



LESSONS FROM THE FIELD

Background

My MAE cohort was split into three groups for the Lessons from the Field (LFF) peer teaching exercise, with eight scholars allocated to my group. Each scholar led an LFF based on their experiences in the MAE program to teach either skills or content that they felt would be of benefit to the group.

I participated in eight LFFs (Table 1). My LFF 'Responding to an outbreak of a new or emerging threat' was the first for our group. I presented this at a video conference on 21 November 2022.

Table 1: Lessons from the field presenters and topics

Presenter	LFF Topic
Maddy Marsland	Responding to an outbreak of a new or emerging threat
Tilda Thomson	Using antimicrobial susceptibility testing and genomic data in <i>Shigella</i> surveillance
Ramona Muttucumaru	Using Bayesian modelling techniques
Amanda Reyes Veliz	What is happening? Where? – Mapping an outbreak in R
Huyen Nguyen	Mapping an outbreak: Plotting cases with specified spatial coordinates to QGIS
Zoe Baldwin	Complexity in enteric outbreak investigations
Patrick Peacock	Visualising Phylogenetic Trees
Phonepasith Bouphe	Using Multi-source surveillance assessment for COVID-19 outbreak

Lessons learned

I learned several key lessons from the process of developing and presenting my LFF including:

- How to decide on a topic that was likely to benefit my audience and how to pitch this at an appropriate level given the diverse backgrounds and experiences of my group.
- How to consolidate responses and pick out the most relevant aspects for further teaching, including highlighting strengths and addressing weaknesses.
- The importance of targeting an evaluation so I could receive feedback that would be useful and beneficial for my future teaching experiences.
- That as a student delivering peer teaching I wasn't expected to have all of the answers or be an expert on the topic, and that it was ok to lean on the experiences of the rest of my group to help move forward the discussion.

I appreciated the interaction and support of my group and received very positive feedback in my evaluation. However, some students reported spending more than 1.5 hours doing my exercise, and this was longer than I had intended. A takeaway lesson from this experience is that in the future I would like to pilot my teaching exercises to ensure they are an appropriate length for different audience members. Overall, I found the LFF a useful exercise, and particularly benefited from the experience of delivering a one hour teaching session at a tertiary education level as I had not done this before.

Acknowledgements

I would like to thank my academic supervisor Anna Glynn-Robinson for critically reviewing my draft LFF and providing constructive input regarding the scope, structure, and questions to include in the evaluation. I would like to thank my field supervisor Janet Strachan for advising how Avian Influenza would be managed within the Victorian context and providing documentation to support the scenario in my LFF. I would like to thank my LFF group for participating and providing feedback on my LFF, with particular thanks to our group coordinator Tilda Thomson.

Self-directed learning session

Lessons from the field: Responding to an outbreak of a new or emerging threat

Background and rationale

COVID-19. Japanese encephalitis. Mpox. What do these diseases have in common?

Over the past few years, Australia has experienced several outbreaks of diseases in which pre-existing immunity within the population was very low or non-existent. All outbreaks are unique, however responding to an outbreak of a disease that is not endemic in Australia can pose additional challenges. There is a suite of public health control measures that can be used when responding to an outbreak, with pre-existing strategies and plans often already in place for targeting control measures. However, when facing an outbreak of a disease that is either new or emerging, these pre-existing strategies and plans may need to be amended or new ones rapidly developed for the response.

During this LFF you will work through a hypothetical case scenario based on recent real-world experiences to consider how you would implement control measures in response to a disease not yet seen in humans in Australia.

Learning objectives:

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

1. Identify appropriate public health control measures and differentiate in what circumstances these would be used
2. Recommend outbreak control measures in response to a case scenario
3. Describe the national governance arrangements for developing guidance and implementing public health controls in Australia

Scenario

You are the senior epidemiologist managing zoonotic diseases at the Victorian Department of Health (DH).

The Department of Jobs, Precincts and Regions (DJPR) informs you that there has been a sudden cluster of deaths in a poultry population in Mildura, with several poultry exhibiting symptoms consistent with Avian Influenza (AI). They have urgently sent samples to a reference laboratory, but results are not expected for 2 – 3 days.

In Victoria, DJPR is responsible for infectious disease outbreaks in animals, but DH is responsible for following up any human contacts and managing disease in humans. DJPR have provided you with a list of possible human contacts at the affected farms. Victoria has previously experienced incursions of AI in poultry, however to date there have been no cases identified in humans.

Task 1

Open the [‘Communicable Diseases Network Australia National Guidelines for Avian Influenza in Humans’](#) (SoNG)

Read the following sections:

7. Case definitions (pages 7 – 8)
11. Contact management (pages 11 – 12)

Then answer these questions:

1. Based on the information that is currently available, how would you recommend managing the individuals DJPR has identified as potential contacts?

An expert panel should be convened by the affected jurisdiction to guide the public health response. The SoNG notes that contacts of infected birds should be rapidly identified, but does not provide a clear definition of who a contact is. The expert panel (and/or jurisdictional protocols) should advise on a contact definition and all potential contacts should be interviewed to assess if they meet the contact definition.

All contacts should be provided with education regarding AI including symptoms to monitor for, and should be provided with the Avian Influenza Fact Sheet (or jurisdictional equivalent) and contact information for the PHU. Where appropriate, contacts should be offered post-exposure prophylaxis with a neuraminidase inhibitor. A virologist should be consulted regarding the use of neuraminidase inhibitors.

All contacts should be placed under surveillance for 10 days following last exposure with the infected birds. Contacts should monitor for symptoms including conducting daily temperature checks. The PHU should communicate with the contact daily to monitor for symptoms. If symptoms develop, the individual should be immediately isolated until medical assessment and testing can be arranged. Contacts and their household members should conduct careful hand hygiene throughout the surveillance period.

2. Are there any other control measures you would consider implementing at this stage?

At this stage there is no evidence of a human case and the SoNG does not require any additional human control measures. Any additional control measures that are implemented should be proportionate to the current risk.

The expert panel may consider some minimally invasive control measures such as exit testing of contacts (i.e. at the end of their surveillance period), asking contacts to avoid high-risk settings, restricting access to affected farms, and increasing environmental cleaning at the affected sites. It would be beneficial to conduct targeted communications with people at risk (e.g. farmers, veterinarians in the region) and alert healthcare professionals to be aware of the potential for suspected cases to emerge.

Scenario

Two days later, the laboratory results confirm that the poultry are infected with influenza H7N7, a strain of highly pathogenic AI. DJPR has reported that more poultry are now displaying symptoms consistent with AI and a second farm has been implicated. Loddon Mallee Public Health Unit (LMPHU) have alerted Mildura hospital to be on the lookout for influenza-like cases and provided them with the human AI national case definition. Later that day Mildura hospital contact you to inform you that three individuals who meet the probable case definition (influenza A infection with epidemiological evidence) have presented to the hospital.

Having read the SoNG, you are aware that transmission of AI from birds to people is considered rare, but you are very concerned about this sudden emergence of cases meeting the case definition. Your initial investigation reveals that all three cases attended the Mildura Show five days prior to their onset of symptoms. This year, the Mildura Show included a petting zoo and a number of animal shows and competitions in which poultry were present.

A joint Incident Management Team (IMT) with DH and DJPR has been established. The IMT has conducted a risk assessment and are seeking your advice on appropriate control measures to implement.

Task 2

During this task you will be asked to consider different control measures that may be implemented in response to a respiratory outbreak, and under what circumstances you would recommend these.

- Write a list of different control measures that may be implemented in response to a respiratory outbreak (these measures should be aimed at human health, list at least four). (Hint: this doesn't need to be specific to AI, think about other respiratory outbreaks you have been involved with).

A number of example control measures are listed in the table below.

The following table provides a framework to think about some of the control measures that may be used to respond to a respiratory outbreak. Now that you have developed your own list, reveal the list we will be working with during this LFF by changing the shading of the table from black to no colour.

- Using your knowledge of different control measures, fill out the column titled 'description' with a high-level summary of what each control measure would usually involve. You may need to do some research to fill these in, definitions are often listed in epidemiology or communicable disease control textbooks. A paper summarising some of these measures is available at [Control Measures for Human Respiratory Viral Infection](#).

THEN

- Consider the scenario, in the column titled 'Avian Influenza' recommend whether or not you would implement this control measure and, if so, justify why and indicate what this would look like in the context of AI.

Note: the first measure is filled out as an example.

Control Measure		Description	Avian Influenza
Movement restrictions	Isolation	<i>Isolation of people or animals with the disease from others who do not have the disease.</i>	<i>Yes – the SoNG recommends isolating cases until they are no longer infectious. For avian influenza you would also isolate sick poultry and animals to prevent the spread of disease.</i>
	Quarantine	<i>Isolation or separation of people or animals who have been exposed to a disease and are at risk of developing the disease, from individuals who have not been exposed to the disease and do not have the disease.</i>	<i>No – contacts are not required to quarantine. However, contacts may be recommended to limit travel and exposure in the community.</i> <i>However – poultry farms that have been implicated may need to quarantine poultry.</i>
	Border closures	<i>Restricting movement of people</i>	<i>No – given there are a small number of human cases and</i>

		<i>or animals between defined geographical borders (e.g. jurisdictional or international).</i>	<i>the risk of human-to-human transmission is low, border closures would not be proportionate to the risk of the current outbreak.</i> <i>However – the expert panel may recommend that contacts under surveillance do not leave the state. Border restrictions for poultry may be considered in consultation with DJPR.</i>
	Restrictions on movements (e.g. 5km limit)	<i>Restricting movement of people or animals based on another limiting factor (e.g. distance).</i>	<i>No – given there are a small number of human cases and the risk of human-to-human transmission is low, restricting movements in the general population would not be proportionate to the risk of the current outbreak.</i> <i>However – movement restrictions for poultry may be considered in consultation with DJPR.</i>
Public health and social measures	Physical distancing	<i>The practice of individuals distancing themselves from others (usually recommended to be 1 – 2 metres from other people).</i>	<i>No - given there are a small number of human cases and the risk of human-to-human transmission is low, physical distancing among the general population would not be proportionate to the risk of the current outbreak.</i>
	Restricting gathering size	<i>Restricting the number of individuals who can gather in a defined type of setting (e.g. indoor, outdoor, public or private setting).</i>	<i>No - given there are a small number of human cases and the risk of human-to-human transmission is low, it would not be proportionate to restrict gathering size for the general population.</i>
	Restricting public settings and workplaces (e.g. schools)	<i>Restricting or enforcing the closure of defined settings or the number of people who can attend defined settings (e.g. requirements to work from home or restrictions on the number of people who can be in an office).</i>	<i>No – given there are a small number of human cases and the risk of human-to-human transmission is low, it would not be proportionate to enforce restrictions in most public settings.</i> <i>However – the expert panel may consider restricting events that could lead to transmission such as agricultural shows or farming auctions.</i>

Medical interventions	Vaccinations	<i>A method to induce an acquired immunological response in a host from a specific pathogen or group of pathogens (i.e. to develop protective immunity against subsequent exposure).</i>	<i>Yes – anyone who is at risk of AI exposure (e.g. working in a setting with poultry) should receive the current seasonal influenza vaccine. This is to prevent against coinfection and recombination of the virus. In the event of a major outbreak, widespread seasonal influenza vaccination may be considered.</i>
	Pre-exposure prophylaxis	<i>The use of treatment prior to potential exposure to prevent development of disease.</i>	<i>No – currently pre-exposure prophylaxis for AI is not recommended in Australia. However, in the event of a significant outbreak current guidelines may be reviewed and updated (e.g. reviewing the SoNG or recommendation of the expert panel). Pre-exposure prophylaxis with neuraminidase inhibitors is recommended in some contexts internationally.</i>
	Post-exposure prophylaxis	<i>The use of treatment following exposure to prevent development of disease or minimise disease severity.</i>	<i>Yes – neuraminidase inhibitors are recommended to be given to contacts, where appropriate, following exposure. This should be done in consultation with a virologist.</i>
PPE and hygiene	Community use of PPE (e.g. facemasks)	<i>Recommendations or requirements for the general population to wear PPE (commonly facemasks) in certain defined or general settings (e.g. ranging from whenever in public to only in high risk environments).</i>	<i>No – given there are a small number of human cases and the risk of human-to-human transmission is low, it would not be proportionate to recommend or require PPE use by the general population.</i>
	Use of PPE in high-risk settings	<i>Recommendations or requirements for the individuals to wear PPE in select high risk settings (e.g. settings with a vulnerable population or where the risk of transmission is high).</i>	<i>Yes – anyone working in affected or high risk settings for transmission (e.g. poultry farms) should wear appropriate PPE and receive training in donning, doffing and disposal of PPE. Depending on the size of the outbreak, the expert panel may also recommend PPE use in vulnerable settings (e.g. RACF), however this would not be recommended at this stage.</i>

	Environmental cleaning	<i>Appropriate cleaning of an environment that may have been contaminated to reduce the risk of transmission (e.g. regular cleaning of poultry farms to reduce the risk of transmission to humans).</i>	<i>Yes – in the context of local transmission an environmental evaluation is recommended and infection control procedures should be reviewed. Transmission can occur via contaminated excretions or fomites in the environment.</i>
	Personal hygiene and handwashing	<i>Encouraging good personal hygiene and handwashing within the general community.</i>	<i>Yes – members of the public should be regularly encouraged to maintain good personal hygiene. In the context of an outbreak, additional targeted communications may be directed to individuals at risk of transmission (e.g. handling animals or contaminated surfaces).</i>
High risk settings and vulnerable communities	Targeted communications	<i>Advice, education, or information directed at specific individuals or groups in the community who are at high risk of acquiring disease (or in some circumstances, those vulnerable to severe disease).</i>	<i>Yes – individuals who are in environments that put them at risk of transmission (e.g. farms) should receive targeted communications. The expert panel may recommend additional communications to the broader community in affected regions.</i>
	Restrictions on entry by general population	<i>Restricting access by the general public to settings that are believed to be at high risk of transmission or with vulnerable individuals who are at high risk of disease.</i>	<i>Yes – in this instance poultry farms would be considered high risk environments for transmission of disease. Individuals should be restricted from accessing these sites unless required and using appropriate PPE. However – it would be premature to restrict access to settings with vulnerable individuals who are at high risk of disease (e.g. RACF) as the risk of human-to-human transmission is limited.</i>
	Restrictions on movements within high-risk settings	<i>Restricting movement within a high risk setting to prevent transmission of disease (e.g.</i>	<i>No - in some settings (e.g. infected farms) it may be appropriate to limit movements to individuals required to be there and who are using appropriate PPE. However, it is</i>

		<i>zoning healthcare facilities).</i>	<i>unlikely that zoning could feasibly be applied in these contexts. It would be more practical to limit exposure to the entire site. The expert panel may apply specific recommendations in some contexts.</i> <i>However – in the event of an outbreak and hospitalised cases, zoning may occur within healthcare settings to prevent human-to-human transmission (e.g. designated staff, designated ward).</i>
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In the context of an outbreak in Victoria, DJPR would be primarily responsible for implementing interventions targeting animal health. However, you may make recommendations to the joint IMT.

6. Are there any recommendations targeting animal health that you would recommend considering in the context of this scenario? (Hint: if you are struggling to think of any, read about how [Agriculture Victoria have previously responded to an outbreak of AI in poultry](#)).

Some of the specific recommendations have been discussed above (e.g. quarantine of exposed poultry, isolation of infected poultry, environmental cleaning of affected farms, restricting inter-jurisdictional poultry movements, targeting communications towards workers involved in these industries).

There are a range of additional animal-specific control measures that could be considered:

- Environmental measures to prevent feed and water from becoming contaminated.
- Restricting poultry movements between farms (i.e. keeping poultry at the same farm for the duration of the outbreak).
- Housing orders for poultry in affected farms or within the region to stay indoors (i.e. to prevent co-mixing between animals in agricultural settings and wildlife).
- Culling of infected poultry and/or exposed poultry.

Scenario

It has now been two weeks since the outbreak in poultry commenced and there have been 9 confirmed human cases of H7N7. Most (n=7) have been associated with the Mildura show, and two cases were in farmers who work with poultry in the Mildura area. The control measures that the IMT has implemented (as recommended in Task 2) seem to be effective, with no new human cases reported in the past 5 days. However, in the past 3 days poultry populations across the border in nearby New South Wales (Wentworth and Pooncarie) and South Australia (Renmark and Loxton) have begun displaying symptoms of AI.

Given the increased threat, your Chief Health Officer (CHO) has asked you to help prepare a paper for the Australian Health Protection Principal Committee (AHPPC) to consider next

steps at a national level. The Communicable Diseases Network Australia (CDNA) would also like to review the AI SoNG and consider additional guidance given the current situation.

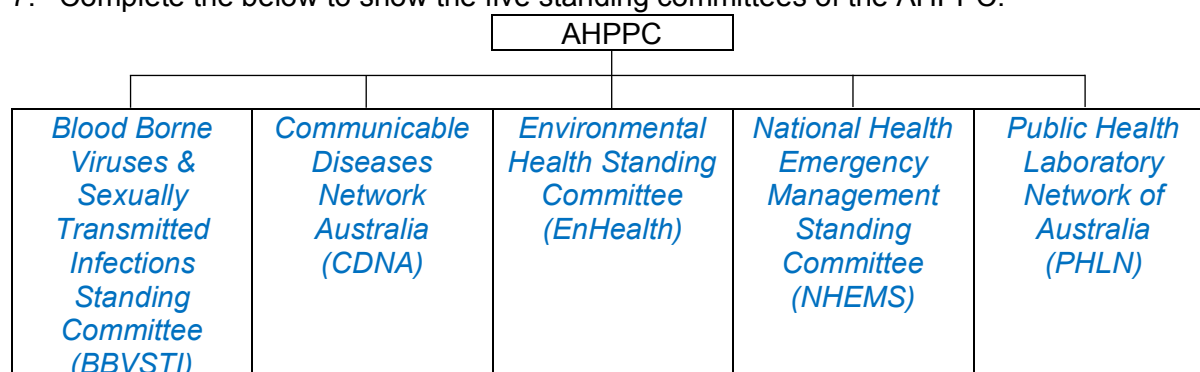
Task 3

The AHPPC play an important role in mitigating emerging health threats in Australia and providing advice to government. As the intelligence lead during a significant outbreak, you may be asked to provide updates or develop advice for AHPPC and its subcommittees.

Some resources to help you complete this section are available below:

- Read about the [Australian Health Protection Principal Committee](#).
- Read about the [Communicable Diseases Network Australia](#).
- Read about the [Series of National Guidelines](#).

7. Complete the below to show the five standing committees of the AHPPC.



8. How is the membership for AHPPC and its sub-committees selected? (hint: there is no need to name members, just list the general categories of members).

AHPPC – Commonwealth Chief Medical Officer, Chief Health Officers from all Australian states and territories, Australian Defence Force Commander Joint Health, Commonwealth Chief Nursing and Midwifery Officer and Deputy Chief Medical Officers. A range of experts and delegates can be invited to attend AHPPC including the chairs of each of the standing committees and advisory groups, the chair of the National Critical Care & Trauma Centre, and the New Zealand Chief Medical Officer, as required.

Representatives from the Commonwealth and each Australian jurisdiction sit on all sub-committees. Membership is made up of relevant expertise (e.g. microbiologists and pathologists sit on PHLN, communicable diseases specialists sit on CDNA). Some committees also have a number of additional invited experts and representatives from key organisations.

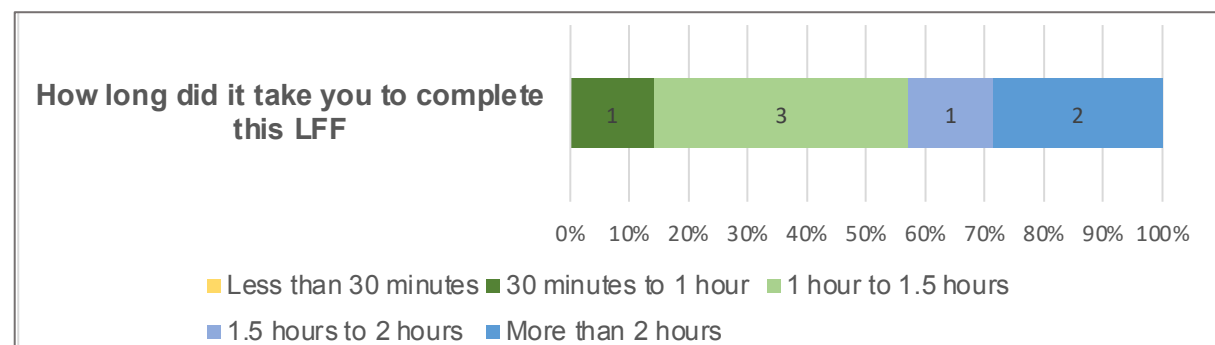
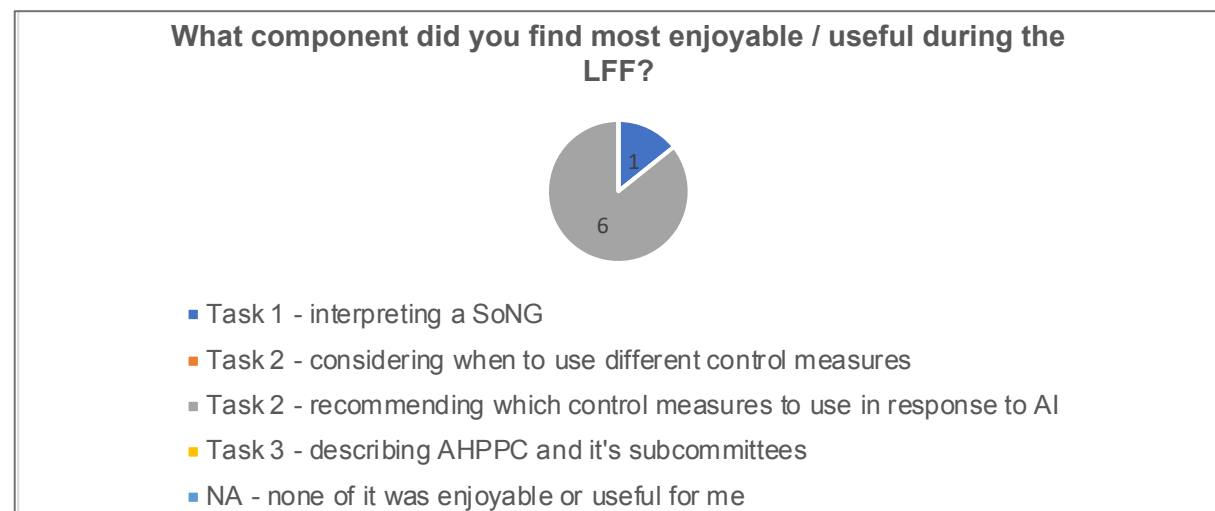
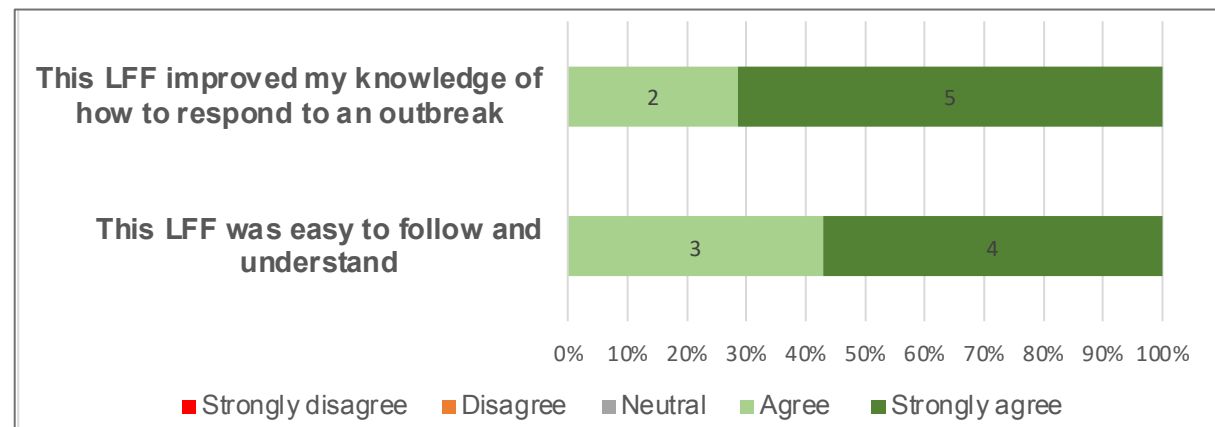
9. You have been asked to sit on a working group⁴ to revise the AI SoNG. Which AHPPC standing committee oversees the SoNGs? What is the process for revising a SoNG?

⁴ A working group is a small group of experts who are brought together to achieve a specific goal. More information on SoNG working groups is available in the listed resources.

The Communicable Diseases Network Australia (CDNA) oversees all SoNGs. SoNGs are typically reviewed for currency every 6 months in line with a CDNA work plan, however can be updated more regularly if required. In this scenario, the CDNA Chair has identified that the SoNG requires review. The next step would be to establish a working group to draft revised changes. The working group will usually be supported by a technical writer from the Commonwealth.

The technical writer will conduct a literature review and draft changes to the SoNG. These changes will be discussed and refined by the working group. Input will typically be sought from PHLN and any other relevant AHPPC standing committees. The final version will be endorsed by CDNA and PHLN (and any other standing committee involved in the revision process). Revised SoNGs are noted by AHPPC prior to publication.

Evaluation



Were there any components that could be improved?

Great work Maddy!

None!

It was very useful to go through public health measures in a different context

None come to mind.

I think it's great!

None! If anything could have had a longer scenario e.g. with a few more developments to respond to

All good. You did the great work.

CHAPTER VII

ADDITIONAL PUBLIC HEALTH AND FIELD PLACEMENT EXPERIENCES

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PREFACE

The MAE program focuses on 'learning through doing'. While the majority of my day-to-day work directly related to the projects that met the four MAE core competencies, I was fortunate to be able to gain a breadth of experience across the broader work of the Public Health Division at the Victorian Department of Health. The remainder of this chapter summarises some of my ongoing roles and responsibilities, and additional projects I have supported during my MAE program. In addition, I was able to participate in a few workshops and training sessions, and the lessons I have learned from these are outlined below.

ADDITIONAL OUTBREAK INVESTIGATIONS

My role

In addition to my outbreak investigations (Chapter 5), I supported the public health follow-up of a range of cases, clusters and outbreaks for notifiable conditions during my MAE. This included supporting the response to measles, meningococcal, salmonella, campylobacter and respiratory outbreaks. Some key examples are outlined below. This involved conducting interviews with cases and contacts, providing public health advice (e.g. coordinating testing, exclusion from work, clearance antibiotics), and inputting data into Victoria's Public Health Event Surveillance System (PHESS).

I was also involved in the early stages of outbreak investigations that did not progress, including campylobacter, rotavirus and congenital syphilis cases. This involved attending meetings, monitoring PHESS for incoming notifications, and being available to support the public health officers in conducting initial investigations.

Furthermore, I observed a number of Incident Management Teams (IMTs) for major outbreaks including Japanese encephalitis (JE), mpox and congenital syphilis. My role within these meetings was usually limited to observing, however I was available to be allocated to ad hoc tasks where additional epidemiology support was required. Notably, the JE IMT requested Tilda and me to complete a literature review which led to my epidemiological study (Chapter 3).

Example 1: A salmonella outbreak associated with Asian/Vietnamese food

In October 2022, approximately 60 cases of *Salmonella Typhimurium* were identified that were genomically related and clustered in time. As the cases were dispersed across Victoria, there was a need to undertake comprehensive case interviews to identify a likely source. I supported the outbreak investigation by conducting case interviews, initially using a trawler food questionnaire, then a standard "chicken and egg" questionnaire. Most cases had eaten some form of Asian or Vietnamese food, and some common restaurants were identified. Environmental sampling was conducted at implicated restaurants, however all food samples were negative for salmonella. The outbreak was considered likely linked to fresh produce or eggs, however no further cases were associated after October and the investigation concluded without a confirmed source.

Example 2: A salmonella cluster in a neonatal Intensive Care Unit

In April 2023, the Department of Health (DH) was notified of two cases of salmonella in neonates in a special care nursery. DH coordinated testing of formula, however the results came back negative for salmonella. I supported the investigation by speaking with the hospital and parents to arrange for faecal sampling, to identify a possible carrier. I also coordinated with the Infection Prevention and Control team when one child was transferred due to unrelated issues. All results were negative and no further cases were identified.

Example 3: Illnesses associated with a dairy farm

In May 2023, DH was notified of a small group of families who had visited a dairy farm in Victoria, with five of the seven visitors becoming unwell after consuming raw milk. All five were young children, with two testing positive for campylobacter and one testing positive for cryptosporidium. I conducted case interviews with one of the families (parents of two of the children) to gain further insights into the circumstances of the dairy farm and other possible exposures. The outbreak was likely associated with the consumption of raw milk. As the raw milk was offered for free as part of an informal tour, there was no legal or regulatory action required as part of the public health response. I provided education on avoiding consumption of raw milk in the future.

Lessons learned

When I commenced my MAE, I expressed a strong desire to be involved with as many different outbreaks as possible, so I could gain experience in different types of outbreaks and better understand the variability and breadth of what can be involved. I gained skills and confidence in talking to cases and contacts, delivering appropriate public health advice, monitoring and tracking the progress of cases, and following the steps of an outbreak investigation in different circumstances. When entering the MAE I was initially concerned that I wouldn't be prepared to manage outbreaks in different settings in the future – how could working on a foodborne outbreak in Victoria possibly prepare me to work on a major measles outbreak in the Pacific or a viral haemorrhagic fever outbreak in Africa? Through my experiences I gained an appreciation of the transferability of core skills and the fact that even within a disease portfolio no two outbreaks are the same. This has helped me build confidence in outbreak investigation and management. I also came to appreciate the different roles and responsibilities of different teams in the Department of Health (DH) and the breadth of stakeholders involved in different types of outbreaks across Victoria.

MANAGING VACCINE PREVENTABLE DISEASE NOTIFICATIONS AND REPORTING IN VICTORIA

Background

My day-to-day work was based within the vaccine preventable disease (VPD) portfolio with the Communicable Diseases and Epidemiology Surveillance unit (CDES). The VPD team is responsible for monitoring all incoming VPD notifications, triaging cases, and referring cases that require public health follow-up. This work also involves identifying potential respiratory outbreaks in residential care facilities.

The VPD team is also responsible for monitoring and reporting on cases and epidemiological trends. This includes delivering a regular report to Victoria's weekly surveillance meeting, and quarterly and annual reports on specific diseases. These meetings are attended by approximately 200 individuals from across the Department of Health (DH) and Local Public Health Units (LPHUs). Each disease portfolio provides key updates and answers questions, requiring a thorough understanding of which cases are of public health importance. The second half of the weekly surveillance meeting focusses on a 'key topic' each week.

My role

I conducted daily sign outs and triaging of incoming VPD notifications. This included monitoring incoming laboratory results and reports from public health officers throughout the day and escalating urgent notifications. I also compiled reports and summaries of VPD notifications and outbreaks, and presented these to Victoria's weekly surveillance meeting, along with the outcomes from my MAE projects. Finally, I supported training of new surveillance officers to do these roles as they joined the VPD team.

Lessons learned

These duties required me to develop a thorough understanding of case definitions, criteria for escalation and public health follow-up, and how to use Victoria's Public Health Event Surveillance System (PHESS). Identifying urgent cases and developing reports for the weekly surveillance meeting required identifying cases of public health importance and being prepared to respond to an array of questions from stakeholders. I developed a comprehensive understanding of diseases within my team's portfolio and the confidence to conduct the day-to-day work of the VPD team.

SCOPING A SURVEILLANCE SYSTEM TO MONITOR VACCINATIONS IN CHILDREN IN CARE SERVICES

Background

In 2015, the Victorian Department of Health (DH) conducted an initial scoping assessment to investigate vaccination rates among children in care services, given the vulnerability of this group and the lack of local evidence. This internal assessment found very low vaccination coverage (~60%) among children in care services. A formal priority was established that '100% of children who enter care services are up to date with the immunisation schedule within six months of their initial assessment'. However, existing vaccine surveillance platforms within Victoria, including the Australian Immunisation Register (AIR), do not support identifying children in care services. Therefore, it has not been possible to formally assess the vaccination rate of children in care services in line with this priority.

Victoria is currently progressing work to establish a new system for data linkage that will support monitoring and evaluation of public health programs. However, the timing for when this will occur remains uncertain and there is a need to benchmark vaccination rates in the absence of this longer-term enduring system.

My role

This project was a priority when I entered DH and I initially progressed this with the intention of it meeting the MAE competency to 'evaluate or establish a surveillance system'. The project sought to provide a benchmark for current vaccination coverage in children in care services and, based on these results, scope potential options and assess the feasibility of establishing a transitional surveillance system to monitor vaccination coverage among children in care services until the longer term linked data system is established.

I developed a project proposal and data analysis plan to support linking datasets from DH and the Department of Families, Fairness and Housing (DFFH). I engaged DFFH, who manage children in care services, and conducted a series of meetings to finalise the project scope and plan. I then supported DFFH to progress developing a Memorandum of Understanding (MoU) to support data sharing, in consultation with legal experts from DH and DFFH. Alongside this, I conducted initial stakeholder interviews to commence scoping the transitional surveillance system, pending the findings of the pilot study. I compiled a list of options which were intended to be presented to the focus group along with the results of the pilot study to support decision making.

Unfortunately, in the final stages of the MoU, DFFH received updated legal advice that a MoU would not be sufficient, and a data sharing agreement under the Heads of Agency agreement would be required to progress this work. This significantly extended the timeline for this project and it was not feasible to complete during my MAE program. As a result of this change, I decided in consultation with my supervisors that it would be more efficient to progress this project through the Centre for Victorian Data Linkage (CVDL) and supported the associated paperwork. As at the conclusion of my MAE program, DH and DFFH are continuing to progress this project.

Lessons learned

This was an important project and a priority for DH. However, progressing the legal and governance requirements were much more complicated than anticipated and it was very disappointing that this prevented me from completing the project. I had invested a substantial amount of time in this project, which impacted my ability to complete the other requirements of the MAE after this project was delayed. From this I learnt valuable lessons about planning my time, being able to admit when things weren't working, and walking away from projects even when I was very invested in the work and outcomes.

Although this project did not end how I had hoped, I gained some valuable skills from progressing this work. This was my first experience in conducting interviews with stakeholders to scope options, which proved very valuable as I transitioned to conducting the evaluation of a surveillance system (Chapter 4). I also gained skills in data linkage and analysis, as I needed to plan how to conduct a probabilistic linkage of the datasets, determine how to classify individuals as fully vaccinated, and I had commenced developing the Stata code for the analysis.

Finally, I found it very surprising that we didn't have an existing system to identify vaccination rates in this at risk population, and when I looked at the available reporting, I noted significant gaps and limitations that weren't adequately conveyed. From this I learned the importance of understanding the limitations in our surveillance systems, including the AIR and how this impacts surveillance, and the need for continuous improvement.

Public health impact

Although I was not able to complete this project, I was able to confirm that this remained a priority for both DH and DFFH and was able to restart negotiations to progress this work in the near future. Once completed, this work will play an important role in ensuring children in care services are fully vaccinated.

DEVELOPING A STATE-WIDE PROTOCOL FOR GROUP A STREPTOCOCCAL DISEASE

Background

Invasive Group A Streptococcal disease (iGAS) became nationally notifiable in 2021 and became notifiable in Victoria in 2022. In early 2023, an increase in iGAS cases, including cases of severe illness, were detected in Victoria. At the time, the Communicable Disease Network Australia (CDNA) was in the process of developing a National Guideline for Public Health Units (SoNG). Whilst this was being finalised, there was an urgent need to collect enhanced surveillance data to inform public health actions for iGAS cases in Victoria.

My role

I supported the development of an enhanced surveillance form (ESF) and draft state-wide protocol for iGAS in Victoria. These documents were based on available literature, protocols from other Australian states and territories, and Victorian protocols for other similar conditions such as Invasive Pneumococcal Disease (IPD). I was not able to finalise this work due to attending an MAE course block. However, in passing this work to the Public Health Medicine team for finalisation, I summarised key findings from my research, and provided advice on what I recommended should and should not be included in the ESF to ensure we collected meaningful data for public health action.

Lessons learned

I had experience in developing public health guidelines prior to the MAE. However, this was an opportunity to consider some of the on-the-ground challenges of implementing guidelines. In particular, I learned the importance of balancing best practice against the associated burden of following up cases. There was also a need to consider the wider capacity of the public health system when deciding what conditions should be prioritised for public health follow-up.

Public health impact

The ESF was finalised and the Department of Health (DH) commenced collecting enhanced surveillance data from iGAS cases in early 2023. The lessons from developing the questionnaire and protocol also supported Victoria's input towards the national SoNG.

TRAINING LOCAL PUBLIC HEALTH UNITS

Background

Throughout my MAE placement, the Victorian public health system was transitioning to a networked system, with conditions being integrated into and managed by Local Public Health Units (LPHUs). This required extensive work updating protocols and delivering training to medical personnel, public health officers and epidemiologists from LPHUs for each condition as it was transitioned. Most VPDs transitioned to being followed up by LPHUs during my MAE placement.

My role

I provided the epidemiological support for the training program on Invasive Meningococcal Disease (IMD). This was the first urgent condition to transition to LPHUs. I developed and delivered the training session on epidemiology of IMD and also assisted the Communicable Disease Prevention and Control (CDPC) team to develop the training on investigation and public health follow-up of IMD. I attended all associated sessions to respond to questions as they arose.

I also supported the transition of a few other VPDs, particularly respiratory outbreaks in residential care facilities. I did this by responding to questions from LPHUs after the transition, and identifying issues in the data entry for VPDs in Victoria's Public Health Event Surveillance System (PHESS), to flag and rectify these issues with LPHUs.

Lessons learned

I found developing and delivering the IMD epidemiology training a particular challenge. I was supporting my supervisor who was on annual leave and needed to balance competing priorities whilst completing this task. I needed to access relevant data through PowerBI, a program I was unfamiliar with, understand how the epidemiology of IMD had changed over time in Victoria, and synthesise this into an interesting and straightforward presentation for a diverse audience. From this I learned the challenges of delivering training on a subject which I myself was learning, and also the benefits of being thrown in the deep end and taking on new responsibilities. I became more confident in my role in the VPD team from this experience.

EPIDEMIOLOGICAL SUPPORT TO VICTORIA'S VIRAL HAEMORRHAGIC FEVER PREPAREDNESS WORKING GROUP

Background

In 2022, an outbreak of Ebola virus disease (EVD) was reported in Uganda. This was the largest outbreak of a viral haemorrhagic fever (VHF) to occur since the COVID-19 pandemic. Within this context, it was recognised there was a need for increased preparedness and the Department of Health (DH) established a VHF preparedness working group, to monitor the escalating outbreak and any future outbreaks of concern, and bring together relevant stakeholders (e.g. hospitals responsible for managing VHF cases) in preparation for managing any local cases.

My role

Tilda Thomson, another MAE scholar, and I were asked to jointly lead epidemiology and intelligence for the VHF working group. We monitored emerging outbreaks internationally and provided regular reports to the working group to inform planning. Had cases occurred locally, we would have been well positioned to be the epidemiologists on the Incident Management Team (IMT), however this did not occur.

Lessons learned

This was a valuable opportunity to be involved in biosecurity and preparedness, and reiterated the importance of outbreak planning and monitoring international sources for epidemiology intelligence.

Public health impact

The working group provided a forum to ensure all relevant stakeholders were aware of their roles and responsibilities, and to review and update local plans. Although no cases occurred locally, these activities ensured that Victoria was well prepared to respond. This work was also important in identifying gaps and priorities for future preparedness work.

ADDITIONAL TRAINING AND WORKSHOPS

Global Outbreak Alert and Response Network (GOARN) training

I participated in the Global Outbreak Alert and Response Network (GOARN) tier 1.5 training 'Orientation to international outbreak response with GOARN and WHO'. This training was designed for individuals who would like to be involved with international deployments in the future. This training provided me with a greater understanding of what would be involved with an international deployment, how to prepare, what to expect, and the process for volunteering within Australia. Whilst I was not able to participate in an international deployment during my MAE, this remains a priority for me in the near future.

EPIWATCH and other digital surveillance methods workshop

I participated in a 2 day workshop on 'EPIWATCH and other digital surveillance methods' run by the University of New South Wales. This workshop supported me to work through an outbreak and bioterrorism scenario occurring at a regional and international level. The practical nature of this exercise provided skills in responding to an emerging threat and developing watching briefs.