

Applied Epidemiology of Infectious Diseases in Queensland, Australia

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

Dr Ashish Chandra Shrestha

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Assoc. Prof. Stephen Lambert

Field Supervisor

Communicable Diseases Branch

Queensland Health



Dr Emma Field

Academic Supervisor

National Centre for Epidemiology
and Population Health



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Declaration

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the Australian National University or any other educational institution, except where due 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.



Ashish Chandra Shrestha

24 October 2023

“The way we work in public health is, we make the best recommendations and decisions based on the best available data”— Thomas R. Frieden

Acknowledgements

It is my privilege to look back and remember many wonderful people, who have made this journey memorable and meaningful. A journey which I thought was beyond the horizon but realised coming to an end when writing this section. I would like to start by expressing my gratitude to Stephen Lambert. Honestly, I would not have started this journey without your genuine advice and guidance. I am grateful to Emma Field for her excellent supervision. It is a lifetime opportunity to have been supervised by both of you and I have enjoyed getting best out of the Master of Philosophy in Applied Epidemiology (MAE) (Field Epidemiology Training Program). I am fortunate to have supervisors for encouraging me to be independent and providing vision to the right direction. I hope to take away such qualities to be able to mentor future public health professionals, researchers, and epidemiologists!

I acknowledge staff at the Communicable Diseases Branch, Queensland Health for their kind welcome. My project accomplishments were possible with an incredible support from the Epidemiology and Research Unit and the Data Services. Many thanks to Frances Birrell, Mohana Rajmohan, Bridget O'Connor, Andrew Lockhart, Mayet Jayloni, Nicole Burt, Ramim Sourjah for providing insights into the surveillance systems. Thanks to other staff who made time to have conversations with me and making me feel a member of the team. I enjoyed learning from OzFoodNet Queensland on foodborne outbreak investigations. Thank you, Russell Stafford and Robert Bell for your guidance on my project and opportunity to be involved in other activities. I would like to thank Robert Ware, Ross Andrews, Craig Thompson, and Dharshi Thangarajah for guiding me on my projects.

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Abstract

I commenced my Advanced Field Epidemiology Training Program (FETP) at the National Centre for Epidemiology and Population Health, the Australian National University with placement at the Communicable Diseases Branch, Queensland Health in February 2022. During the placement, I was involved in multiple projects, which demonstrated my core competencies to meet the requirements of the program including conducting an analysis of a public health dataset; investigating an acute public health problem or threat; designing and conducting an epidemiological study; and evaluating a surveillance system.

The projects and their findings are presented in this thesis as different Chapters: Epidemiology of varicella-zoster virus in Queensland, 2010–2021; An investigation of Shiga toxin-producing *Escherichia coli* notifications in Queensland, 2020–2022; Using genomic surveillance for the investigation of COVID-19 clusters of a distinct sub-lineage of SARS-CoV-2, Queensland, 2023; Influenza epidemiology and vaccine effectiveness following public funding of an influenza vaccine program in Queensland, 2022; and an Evaluation of surveillance for acute flaccid paralysis in Queensland.

The thesis also describes my other experiences and public health activities including teaching to peers and first year students, presentation to scientific audiences at conferences, conducting a literature review, writing a lay summary on one of my field experiences, and participating in various departmental activities and meetings. These projects and activities are as per the requirements of the FETP undertaken for the degree of Master of Philosophy in Applied Epidemiology of the Australian National University.

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List of abbreviations

ABS	Australian Bureau of Statistics
AFP	Acute Flaccid Paralysis
AIR	Australian Immunisation Register
ANU	Australian National University
APSU	Australian Paediatric Surveillance Unit
ASPEN	Australian Sentinel Practices Research Network
CDB	Communicable Diseases Branch
CI	Confidence Interval
COVID-19	Corona Virus Disease
DNA	Deoxyribonucleic Acid
DTP	Diphtheria Tetanus Pertussis
FETP	Field Epidemiology Training Program
FLUCAN	Influenza Complication Alert Network
FSS	Forensic and Scientific Services
HHSs	Hospital and Health Services
HUS	Haemolytic Uraemic Syndrome
IgG	Immunoglobulin G
IRR	Incidence Rate Ratio
IS	Inter-Seasonal
ISO	International Organisation for Standardisation
MAE	Master of Philosophy in Applied Epidemiology
MLVA	Multiple Locus Variable-Number Tandem Repeat Analysis
MMR	Measles Mumps Rubella

MMRV	Measles Mumps Rubella Varicella
mRNA	Messenger Ribonucleic Acid
NCIRS	National Centre for Immunisation Research and Surveillance
NERL	National Enterovirus Reference Laboratory
NIP	National Immunisation Program
NoCS	Notifiable Conditions System
OR	Odds Ratio
PAEDS	Paediatric Active Enhanced Disease Surveillance
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Vaccine
PCVA	Proportion of Cases Vaccinated
PEP	Polio Expert Panel
PHUs	Public Health Units
PPV	Proportion of Population Vaccinated
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QLD	Queensland
R	Ratio
RR	Relative Risk
S	Seasonal
SA1	Statistical Area 1
SA2	Statistical Area 2
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SNPs	Single Nucleotide Polymorphisms
SPL	Specialty Pathology Laboratory

STEC	Shiga Toxin-producing <i>Escherichia coli</i>
Stx	Shiga Toxin
VE	Vaccine Effectiveness
VE _{adj}	Adjusted Vaccine Effectiveness
VOC	Variants of Concern
VOI	Variants of Interest
VUMs	Variants Under Monitoring
VZV	Varicella-Zoster Virus
WGS	Whole Genome Sequencing
WHO	World Health Organization
WHOCC	World Health Organization Collaborating Centre

Chapter I:

Introduction to field placement and summary of experiences

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1. Field placement

I was offered Master of Philosophy in Applied Epidemiology (MAE) scholar position at the Communicable Diseases Branch (CDB), Queensland Health. It was a great pleasure meeting my academic and field supervisors on the first day of my field placement. We discussed MAE supervisor and student expectations, projects for the training program, and on organising regular meetings. I really felt supported obtaining useful advice and planning to meet the course requirements. My field supervisor introduced me to the Epidemiology and Research Unit team at the weekly notifications meeting (reporting notifiable diseases in Queensland). I was excited to meet staff who had wealth of knowledge and experience in epidemiology and public health.

Queensland's health system is managed by the Minister for Health, Mental Health and Ambulance Services, and Minister for Women through the Department of Health and Queensland's Hospital and Health Boards (1). The Department of Health is managed by the Director-General (1). Queensland Public Health and Scientific Services within the Department of Health includes Cancer Screening Branch, Pathology Queensland, CDB, Health Protection Branch, Forensic and Scientific Services, Biomedical Technology Services, Healthcare Regulation Branch, and Office of Hospital Sustainability (2). The CDB includes a number of units: Blood Borne Viruses and Sexually Transmissible Infections, Communicable Diseases and Infection Management, Epidemiology and Research, Immunisation Program, Information Communications Technology Portfolio Management, and Office of the Executive Director (3).

The responsibilities of the CDB include (4):

- Surveillance, prevention, and control of communicable diseases in Queensland.
- Lead state-wide planning and co-ordination of programs and services to prevent and control communicable diseases, including pandemic and biosecurity planning.
- Conduct state-wide surveillance of a range of communicable diseases, including monitoring trends, detecting outbreaks, and providing a response and monitoring to ensure the effectiveness of disease control activities.
- Co-ordinate and manage the purchase and distribution of vaccines across Queensland.

Data related to surveillance, prevention, and control of communicable diseases in Queensland are collected and maintained by the CDB (5). The Executive Director of the CDB is the delegated custodian of the data on notifiable conditions, vaccination and the needle syringe program, and healthcare associated infections (5).

The frontline public health system in Queensland operates within the public health units (PHUs) located within 16 Hospital and Health Services (HHSs) across the state (6). PHUs focus on protecting health, preventing disease, illness and injury, and promoting health and wellbeing at a population or whole of community level (6). Some PHUs provide services for more than one HHS. There are 14 PHUs: Metro North (Brisbane North), Metro South (Brisbane South), Tropical Public Health Services (Cairns), Central Queensland (Rockhampton), Darling Downs (Toowoomba), Gold Coast, Mackay, North-West (Mount Isa and Gulf), Sunshine Coast, Torres and Capes, Townsville, West Moreton (Ipswich), Wide Bay (Bundaberg), and Wide Bay (Hervey Bay) (6).

2. Field projects

The core competencies I acquired during the MAE program included:

2.1. Analysis of a public health dataset

2.1.1. Epidemiology of varicella-zoster virus in Queensland, 2010–2021

I conducted a case series study using notified cases of varicella-zoster virus (VZV) infection in Queensland from January 2010–December 2021. I performed descriptive analysis and interpreted the results based on intermittent enhanced surveillance of VZV. The study demonstrated the impact of chickenpox and shingles vaccines funded under National Immunisation Program, which resulted in declines in notification rates among age-specific cohorts eligible to receive funded vaccines.

2.2. Investigation of an acute public health problem or threat

2.2.1. An investigation of Shiga toxin-producing *Escherichia coli* notifications in Queensland, 2020–2022

A retrospective review of all Shiga toxin-producing *Escherichia coli* (STEC) cases notified in Queensland from 2020–2022 was conducted to understand the significance of cases notified from a specialty pathology laboratory servicing alternative health practitioners. I took on the role of an investigator from conducting a detailed epidemiological review to preparation of a report for dissemination. This study highlighted a need for revision of STEC guidelines including giving consideration to factors such as disease severity, outcome, transmission, and laboratory test results when implementing a public health response.

2.2.2. Using genomic surveillance for the investigation of COVID-19 cluster of a distinct sub-lineage of SARS-CoV-2, Queensland, 2023

A cluster of COVID-19 cases related to a distinct sub-lineage of the Omicron strain was notified by the Forensic and Scientific Services, Queensland Health to the CDB. I took on the role of a lead investigator; identified the source of infection for cases and sub-clusters; undertook the data analysis; and drafted a final report. This Chapter highlighted the importance of infection prevention and control measures in high-risk settings to prevent further virus transmission.

2.3. Design and conduct an epidemiological study

2.3.1. Influenza epidemiology and vaccine effectiveness following public funding of an influenza vaccine program in Queensland, 2022

I conducted a literature review to understand the context of influenza vaccine effectiveness in Queensland. I was involved in developing study designs, data management, data cleaning, and performing descriptive and statistical analyses. Influenza vaccine effectiveness was estimated based on a case-control study design using individuals with a negative COVID-19 test as controls. The study highlighted seasonal trend of influenza and estimated influenza vaccine effectiveness among all age groups during the 2022 seasonal influenza epidemic in Queensland.

2.4. Establish or evaluate a surveillance system or other health information system

2.4.1. An evaluation of surveillance for acute flaccid paralysis in Queensland

I designed and conducted a mixed-method study for the evaluation of acute flaccid paralysis (AFP) surveillance in Queensland. The evaluation was based on data analysis and after discussion with the key stakeholders. I prepared a final report for dissemination to the stakeholders and decision makers. Recommendations were made to either remove AFP from notifiable conditions list or improve elements of AFP surveillance in Queensland.

3. Other competencies

3.1. Literature review

I conducted a literature review titled 'Estimates of influenza vaccine effectiveness and efficacy, Australia'. The review focussed on different study designs and estimates of influenza vaccine effectiveness and efficacy in Australia in the last 10 years (2013–2022).

3.2. Lay summary

I wrote a lay summary on my experience at the Metro South PHU, Queensland Health, where I conducted COVID-19 cluster investigation and had an opportunity to explore wider context of public health systems in Queensland. The summary was published as a research story on the Australian National University, National Centre for Epidemiology and Population Health webpage.

3.3. Conference presentations

I gave following oral presentations at conferences:

- The epidemiology of chickenpox and shingles in Queensland in the vaccination era at the Communicable Diseases and Immunisation Conference, Perth, held on 19–21 June 2023.
- Using intermittent enhanced surveillance to better understand varicella-zoster virus epidemiology — Queensland, 2010–2021 at the 1st SAFETYNET Conference, Canberra held on 12–15 September 2023 (Awarded the Best Short Oral Presentation).

3.4. Peer-reviewed publications

I drafted following manuscripts for publication in peer reviewed journals:

- Shrestha AC, Field E, Rajmohan M, Lambert SB. Assessing the impact of chickenpox and shingles vaccination using intermittent enhanced surveillance in Queensland, Australia. *Vaccine*. 2023 Dec;41(50):7539-7547. doi: 10.1016/j.vaccine.2023.11.015
- Shrestha AC, Stafford R, Bell R, Jennison AV, Graham RMA, Field E, et al. Shiga toxin-producing *Escherichia coli* diagnoses from health practitioners, Queensland, Australia. *Emerging Infectious Diseases*. 2024 Jan;30(1):199-202. doi:10.3201/eid3001.231202.3

3.5. Lessons from the field and teaching activities

3.5.1. Lessons from the field

I shared my learning experience from the epidemiological project with my MAE cohort on “Understanding an epidemiological concept of vaccine efficacy and effectiveness”. This was aimed to understand different epidemiological study designs in estimating vaccine effectiveness.

3.5.2. Teaching field epidemiology

I worked in a group of my MAE cohort to develop a lesson plan and teach on an assigned topic on “An outbreak of arboviral infection in East-Arnhem land” to the first-year cohort. I was involved in teaching following topics to the students: Arboviruses and arboviral surveillance, descriptive epidemiology and line list, and epi curve and its interpretation.

4. Coursework

I completed the following five courses of the MAE program:

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

5. Additional field placement activities

In addition to the completion of above core requirements and coursework of the program, I participated in the following activities and meetings during my field placement:

- Field experience at the Metro South PHU for the investigation of COVID-19 cluster.
- Preliminary investigation of decline in fourth dose pneumococcal vaccine coverage among Aboriginal and Torres Strait Islander children in Queensland.
- Supported OzFoodNet Queensland with interviewing cases related to *Salmonella* Typhimurium MLVA 03-13-07-09-523.
- OzFoodNet multi-jurisdictional outbreak investigation teleconference.
- Communicable Diseases Branch weekly notifications meetings.
- Metro South PHU Communicable Disease Control meetings.
- Queensland STEC guidelines working group meetings.
- Presentation at the National Centre for Immunisation Research and Surveillance meeting on the epidemiology of VZV in Queensland (8 December 2022).
- Presentation on proposal of evaluation of surveillance for AFP in Queensland at the Polio Expert Panel meeting (11 April 2023).
- Presentation at OzFoodNet face to face meeting on an investigation of STEC notifications in Queensland (30 May 2023).
- Presentation at Queensland STEC Guidelines Working Group meeting on an investigation of STEC notifications in Queensland (29 June 2023).

6. Summary of MAE program requirements

A summary of my projects and competencies demonstrating fulfilment of the MAE program is shown in the table below.

Table. Summary of the core and minor competencies of the MAE program

Requirements	Chapters					
	2	3	4	5	6	7
Data analysis	✓	✓	✓	✓		
Acute public health problem		✓				
Epidemiological study			✓			
Evaluate surveillance system				✓		
Literature review			✓			
Lay Summary						✓
Conference presentation						✓
Teaching activities					✓	
Other public health activities						✓
Peer-reviewed publication	✓	✓				

✓: requirements completed in the respective Chapters

7. References

1. Queensland Health. Queensland Health organisational structure [Internet]. Brisbane: Queensland Health; 2022 [cited 2022 Mar 31]. Available from: <https://www.health.qld.gov.au/system-governance/health-system/managing/org-structure>
2. Queensland Health. Organisational structure [Intranet]. Brisbane: Queensland Health; 2022 [cited 2023 Aug 23]. Available from: https://qheps.health.qld.gov.au/__data/assets/pdf_file/0030/577524/230523-Department-of-Health-Organisational-Structure.pdf
3. Queensland Health. Communicable Diseases Branch [Intranet]. Brisbane: Queensland Health; 2022 [cited 2023 Jul 23]. Available from: <https://qheps.health.qld.gov.au/qphass/about/branches/cdb>
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5. Queensland Health. Release of data from the Communicable Disease Branch - Guidelines for applicants [Internet]. Brisbane: Queensland Health; 2019 [cited 2022 Mar 31]. Available from: https://www.health.qld.gov.au/__data/assets/pdf_file/0030/1115877/Department-of-Health-Annual-Report-2020-2021.pdf
6. Queensland Health. Public health units [Internet]. Brisbane: Queensland Health; 2020 [cited 2023 Sep 24]. Available from: <https://www.health.qld.gov.au/system-governance/contact-us/contact/public-health-units>

Chapter II:

Analysis of a public health dataset

Epidemiology of varicella-zoster virus in Queensland, 2010–2021

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Prologue

One of the responsibilities of the Communicable Diseases Branch, Queensland Health include surveillance of communicable diseases in Queensland. Time limited, intermittent enhanced surveillance of notified cases of varicella-zoster virus (VZV) infection was undertaken as an initiative within the branch to better understand VZV epidemiology. A study was conducted to determine specific clinical presentation (chickenpox or shingles) in specific age groups and understand impact of vaccination programs.

My role

This Chapter was my first project to demonstrate competency in the analysis of public health data. I commenced the project by conducting a literature review to understand the epidemiology of VZV infection in Queensland. Initially, I drafted a concept note for the project which was developed further to a research proposal. I also drafted an ethics application for submission to the Metro North Queensland Health Ethics Committee. I revised the protocol after review from the committee. I liaised with the Epidemiology and Research Unit and the Data Services at the Communicable Diseases Branch to obtain approval from the Data Custodian.

Prior to performing the descriptive analysis of VZV notifications in Queensland, I was involved in data cleaning and management. I wrote Stata commands for statistical analyses. I generated interactive charts using Microsoft Power BI for initial data visualisation and created tables and graphs. I interpreted the results and discussed the findings with my supervisors for writing this Chapter. Overall, I was responsible for the timely completion of the project from initial project development to revision of final draft of the Chapter under the supervision of my field placement and academic supervisors.

Lessons learned

Surveillance data are collected with an aim to understand the burden of disease and to take appropriate public health actions. Data collection is dependent on the priority given to the condition, which then determines allocation of resources. It is a challenge to analyse a dataset with missing data for variables of interest. A lesson learned was that, whilst a limitation, missing data may be excluded from analysis if the proportion of observations with missing data are small in number or can be circumscribed in time periods. Descriptive analyses can be performed for a specific period or periods for which data are available from targeted follow up or enhanced surveillance. However, precautions should still be taken on the approach for handling missing data. It is important to acknowledge the limitations of the available data when interpreting the results.

An important lesson learned was that a case series study includes only cases and does not involve a formal control group for comparison. Therefore, whilst useful for observing trends and developing hypotheses, no causal inference can be made about the relationship between outcomes and exposures. Statistical analysis should be limited to the descriptive reporting given the nature of the study design. The other lesson was understanding the distribution of data and applying appropriate statistical analyses.

Public health impact

With this project I sought to better understand the burden of VZV in Queensland and highlight the importance of interventions to control the diseases. Vaccine preventable diseases should be monitored to understand disease trends with the implementation of a vaccination program, to allow for better targeting to specific populations. Intermittent enhanced surveillance is useful to obtain further information of laboratory notified cases, however, this requires additional time and resources.

Acknowledgements

I thank my supervisors for identifying this suitable project to develop my knowledge and skills in the analysis of public health data. Completion of this project has given me confidence to develop similar projects on other infectious diseases from designing a case series study to performing descriptive analysis. I appreciate the support of the Epidemiology and Research Unit and the Data Services at the Communicable Diseases Branch for helping me understand the surveillance system in Queensland, data collection process, and providing the data for analysis. I also appreciate the support I have received from the Australian National University teaching staff during course blocks which equipped me with data analysis skills to be able to complete this project.

Abstract

Introduction: Varicella-zoster virus (VZV) is the causative agent of chickenpox and shingles. Chickenpox affects mostly children and shingles those ≥ 50 years of age. This study was aimed to determine the overall trend of VZV notifications in Queensland, determine clinical presentation in specific age-groups, and observe changes in epidemiology following chickenpox and shingles vaccination programs.

Methods: This case series study used notified cases of VZV infection in Queensland from January 2010 to December 2021. In Queensland, most VZV notifications are received as clinically unspecified cases from pathology laboratories. Intermittent enhanced surveillance was conducted by following up clinicians to determine chickenpox and shingles clinical presentations, and these were analysed by age-group, time period, and within vaccine eligible cohorts.

Results: Of the 87,759 VZV notifications received, 70% ($n=61,298$) were notified as unspecified followed by 23% shingles ($n=19,927$), and 7% chickenpox ($n=6,534$). The percent change in notification rate adjusted by age and sex was estimated to be an increase of 5.7% (95% CI 4.9–6.4) each year. Chickenpox notifications fell sharply at 18 months (age timepoint for single dose of chickenpox vaccine), down by 57% and 36% among those aged 18–23 months compared to 12–17 and <12 months of age, respectively. Assuming all cases aged 60 years and older were shingles, the rates decreased by 12–22% among 70–79 years old (eligible for shingles vaccination) over the years 2017–2021 following vaccine introduction in 2016.

Conclusion: The VZV notification rate has increased year on year in Queensland. Impact of chickenpox and shingles vaccines funded under National Immunisation Program is seen with declines in notification rates among eligible age-specific cohorts. Better control may be possible by introduction of a second dose of chickenpox vaccine in childhood and use of more effective shingles vaccines.

1. Background

Varicella-zoster virus (VZV) is a human herpesvirus 3 and the causative agent of the clinical conditions varicella (chickenpox) and herpes zoster (shingles) (1). The virus is highly contagious and spreads through contact or by respiratory route (1, 2). In 2014, chickenpox was estimated to cause 4.2 million severe complications leading to hospitalisation and 4,200 deaths per year, globally (3, 4). In high income countries, chickenpox is more common in children (>90% occurring before adolescence) and is less severe than shingles (4). There were approximately 240,000 cases, 1,500 hospitalisations, and 7–8 deaths due to chickenpox reported annually in Australia before the availability of chickenpox vaccine (5). The World Health Organization recommends introduction of vaccination against chickenpox in the routine childhood immunisation program after assessing the disease burden through surveillance (4).

In November 2005, a publicly funded single dose of chickenpox vaccine was introduced to the National Immunisation Program (NIP) for infants aged 18 months (Table 1) (6). A single adolescent catch-up dose of vaccine was provided to non-immunised or non-infected children aged 12–13 years under school-based programs from 2006 (6). Across Australia, there was a 69% decline in the hospitalisation rate among children of 1.5–4 years of age in the first 2.5 years after implementation (7). The vaccine uptake increased from 6% (monovalent chickenpox vaccine was first registered for use in Australia in June 1999, prior to introduction under the NIP) at 24 months of age to 82% by 2009 and to 92% by 2015 (after the introduction of a mumps, measles, rubella, and varicella combination vaccine) (6). The vaccine effectiveness against hospitalisation for a single dose chickenpox vaccine has been estimated to be 64.7% (6). A Queensland study demonstrated reduction in chickenpox hospitalisation by 70% in 2011–2014 (post-funded vaccination period) (8). Hence, there is good evidence of the effectiveness for the chickenpox vaccine preventing severe disease in the Australian context. However, whilst it is known that one dose schedules reduce morbidity and mortality due to chickenpox, they do not prevent transmission and outbreaks (4). Surveillance of chickenpox is necessary after vaccine introduction to monitor the disease burden and vaccine effectiveness.

The incidence of shingles has been gradually increasing over time in Australia (9). It was estimated to be 10 per 1,000 persons per year for the age group ≥ 50 years compared to 2.5 per 1,000 persons for < 50 years over the period 2000–2006 (10). Exposure and natural infection with VZV is considered to boost immunity against shingles reducing the risk of reactivation (9). The increase in shingles cases has been attributed to waning immunity that occurs with increasing age, along with the increase in ageing in the Australian population (9). As shingles is associated with a high risk of hospitalisation and complications, shingles vaccination has been recommended for the older population (8, 11).

Under the Australian National Shingles Vaccination Program, since 2016 the funded shingles vaccine has been provided to adults aged 70 years with a catch-up program for people aged 71–79 years in place until 31 October 2023 (Table 2) (12, 13). The impact of vaccination has been demonstrated by 13.6% per year decline in prescriptions for antiviral shingles treatment (12), suggesting a decrease in the incidence of the disease (14) .

Infection with VZV is a laboratory notifiable condition in Queensland (15). The majority of the cases notified in Queensland are not accompanied with information on the associated clinical syndrome, either chickenpox or shingles, and are categorised as unspecified (16). In Queensland, notifications in children aged <8 years were previously followed up with clinicians to confirm the clinical presentation as chickenpox or shingles (16). Cases were followed up from January 2018 among children <10 years and adults ≥60 years as a part of project agreement with the Commonwealth Government for vaccine preventable diseases surveillance program (2014–2020) (16–18). Time limited enhanced surveillance was conducted from 01 December 2017 to 30 September 2018 (followed up for one month in each quarter) and from 01 August 2019 to 31 December 2020 for all notified cases (16). With this study, we aim to determine the overall trend of VZV notifications, use enhanced surveillance data to determine clinical presentation of disease in specific age groups during the follow up periods, and observe changes in notification epidemiology following vaccine introduction.

Table 1. Chickenpox vaccination in Australia (19)

Month and Year	Intervention	Target age group
June 1999	First chickenpox vaccine registered for use	≥9 months
December 2002	Second chickenpox vaccine registered for use	≥12 months
September 2003	A single dose of chickenpox vaccine recommended	18 months
	A single dose of chickenpox vaccine recommended with no history of chickenpox vaccination or clinical disease	10–13 years
October 2005	First measles-mumps-rubella-varicella vaccine registered for use	>9 months and adults
November 2005	Funded national immunisation commenced with a single dose of chickenpox vaccine	18 months
February 2006	Funded school-based catch-up program commenced with routine vaccination with no history of chickenpox vaccination or clinical disease	10–13 years
March 2006	Second MMRV vaccine registered for use	12 months–12 years
July 2013	MMRV recommended and funded for the single dose of chickenpox vaccine	18 months
December 2017	Funded adolescent school-based vaccination program ceased	10–13 years

*MMRV: Measles, Mumps, Rubella, and Varicella vaccine

Table 2. Shingles vaccination in Australia (20)

Month and Year	Intervention	Target age group
March 2006	First live shingles vaccine (frozen formulation) registered for use	≥60 years
May 2007	First live shingles vaccine (refrigerated formulation) registered for use	≥50 years
July 2009	A single dose of shingles vaccine recommended	≥60 years
October 2013	First live shingles vaccine available on private prescription	—
November 2016	Funded national program commenced with a single dose of shingles vaccine	70 years
	Five-year funded national catch-up program commenced	71–79 years
July 2018	First inactivated recombinant shingles vaccine registered for use	≥50 years
June 2021	First inactivated recombinant shingles vaccine available on private prescription	—
October 2021	Catch-up program extended until 31 October 2023	71–79 years

2. Methods

2.1. Study design

This is a case series study including notified cases of VZV infection from January 2010 to December 2021 in Queensland. The duration of the study allowed examination of the notification rates and trend over eleven years.

Case definitions

VZV infection is a notifiable disease in Queensland under the Public Health Act 2005 and the Public Health Regulation 2018 (21). Both confirmed and probable cases are notified (22).

Chickenpox confirmed cases include those identified based on 1) laboratory definitive evidence AND clinical evidence OR 2) clinical evidence AND epidemiological evidence (22). Laboratory definitive evidence requires either isolation of virus from lesions OR detection of antigen by direct fluorescent antibody OR detection of nucleic acid by PCR OR IgG seroconversion. Clinical evidence includes acute onset of a diffuse maculopapular rash developing into vesicles and forming crusts. Epidemiological evidence is when there is contact between two people (one of them is likely to be infectious and the other has illness after contact and at least one of the cases is laboratory confirmed). Probable chickenpox cases are identified based on clinical evidence only (22).

Shingles confirmed cases are identified based on laboratory evidence (isolation of virus OR detection of virus by nucleic acid testing OR detection of antigen by fluorescent antibody) AND

clinical evidence (22). Clinical evidence includes a vesicular skin rash with a dermatomal distribution that may be associated with pain in skin areas supplied by sensory nerves of the dorsal root ganglia (22). Probable shingles cases are also identified based on clinical evidence only (22).

VZV infection unspecified (not elsewhere classified) includes cases confirmed based on laboratory evidence only (isolation of virus OR detection by nucleic acid testing OR detection of antigen by direct fluorescent antibody OR IgG seroconversion) in the absence of clinical presentation information (22).

2.2. Data sources

The Queensland Health Notifiable Conditions System (NoCS) receives VZV notifications electronically from pathology laboratories in Queensland (22). Intermittent enhanced surveillance was conducted by the Communicable Diseases Branch, Queensland Health to determine clinical presentation among specific age groups and periods (Figure 1) (16).

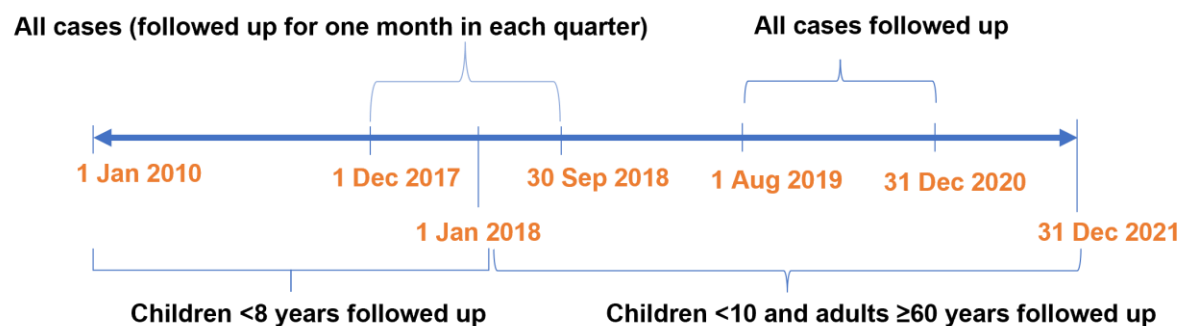


Figure 1. Intermittent enhanced surveillance timeline for notified VZV infection, Queensland, 2010–2021

Enhanced surveillance for specific age groups was conducted as a part of a project agreement with the Commonwealth Government for vaccine preventable diseases surveillance (2014–2020) (17, 18). The agreement committed funding support from the Commonwealth Government to states and territories for providing high quality data on nationally notifiable vaccine preventable diseases as per the core National Notifiable Diseases Surveillance System and enhanced data specifications as agreed by the Communicable Diseases Network Australia (17). Time limited, enhanced surveillance of all notified cases was undertaken as an initiative within the Communicable Diseases Branch to better understand VZV epidemiology.

Enhanced surveillance was performed by contact with the notifying clinicians for non-hospitalised cases, using a form to identify clinical presentation (chickenpox or shingles). The

clinical presentation of hospitalised cases was identified based on clinical or electronic medical record notes and/or discharge diagnosis coding. Hospitalisation status (VZV as primary reason for hospitalisation or any reason for hospitalisation) was updated in NoCS based on hospital morbidity coding data received quarterly from the Statistical Services Branch, Queensland Health via Queensland Hospital Admitted Patient Data Collection to determine specific clinical presentation.

Population estimates

Age-specific mid-year population of Queensland was based on estimated resident population by single year of age, Queensland (Catalogue no. 3101.0 National, state and territory population) obtained from the Australian Bureau of Statistics (ABS) to calculate notification rates (23). Cohort denominator for calculation of shingles notification rate was constructed based on date of birth and age eligibility of shingles vaccination program.

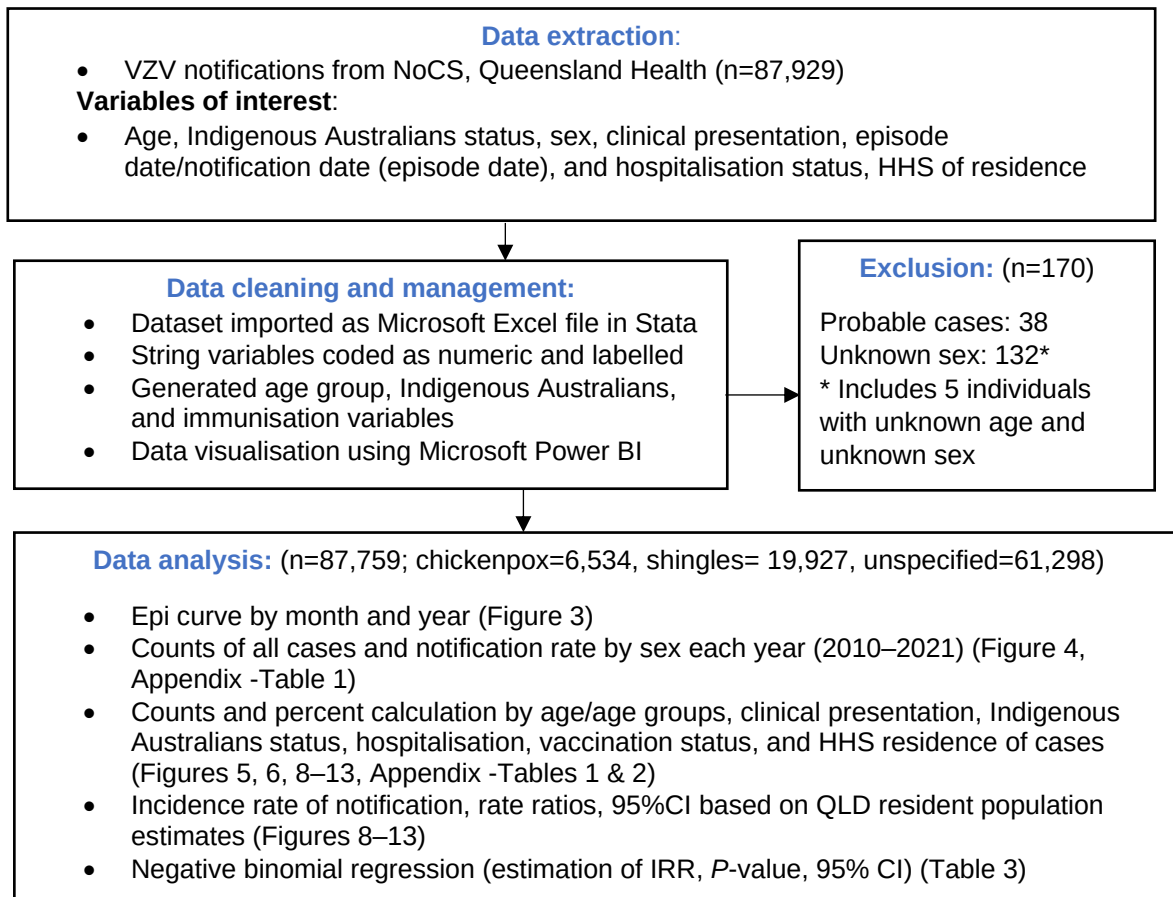
2.3. Data analysis

Counts and percentages of confirmed cases by year, age group, sex, clinical presentation, Aboriginal and Torres Strait Islander status, hospitalisation status, vaccination status, and Hospital and Health Service (HHS) residence of cases were calculated. Enhanced surveillance data for children <8 years were analysed by age in months to understand the impact of vaccination. Episode date (earliest of the following dates in the system: onset date, lab specimen collection date, diagnosis date, notification received date) was considered as the notification date for the analysis. Age was calculated at the time of notification using date of birth and episode date. Age groups were defined based on vaccination strategies and enhanced surveillance. Similar age categories have been used in the Queensland reports of vaccine preventable diseases for VZV infection (16).

The quality of the follow up for clinical presentation was assessed by determining the proportion of notified cases who remained unspecified. The proportion of unspecified was compared with the overall notifications during the study period. Cases with the unspecified clinical presentation were excluded from the analysis of enhanced surveillance data. All cases aged 60 years and older were assumed as shingles for the specific analysis among the age group. Cases who were identified as Aboriginal and/or Torres Strait Islander people were categorised as Aboriginal and Torres Strait Islander people (hereafter respectfully referred to as Indigenous Australians). Notifications with Indigenous status missing or not clearly defined were categorised as unknown. Completeness of Indigenous Australians status was determined by calculating the proportions of notifications with unknown status. Inclusion of

Indigenous Australians status for analysis (notification rate and incidence rate ratio) was considered after determining an acceptable level of completeness of Indigenous Australians status (at least 70%) in line with the threshold used in national reporting (24). Confirmed cases were included and probable cases, cases with unknown sex and cases with unknown date of birth or age were excluded prior to the analysis (Figure 2).

Notification rates per 100,000 population per year were calculated for specific year, age, sex, Indigenous Australians status, and hospitalisation based on ABS-midyear population. Incidence rates by HHS were calculated based on ABS modified data derived by the Statistical Analysis Linkage Team, Statistical Services Branch, Queensland Health (25). Negative binomial regression was performed to calculate incidence rate ratios, *P*-values and 95% confidence intervals adjusted by age and sex over the study period. Seasonal pattern of VZV infection was determined by Edward's model (26, 27). Data management and analysis were performed using Microsoft Excel Version 2202 (Microsoft, Redmond, Washington), Stata version SE 16.1 (StataCorp, College Station, TX), and QGIS 3.28 (QGIS Association). The analysis of the study involved following steps as shown in Figure 2.



VZV: Varicella Zoster Virus; NoCS: Notifiable Conditions System; HHS: Hospital and Health Services; QLD: Queensland; IRR: Incidence Rate Ratio

Figure 2. Flowchart for the data analysis of VZV notifications in Queensland, 2010–2021

2.4. Ethics and other approvals

Ethics approval was obtained from Queensland Health, Metro North Human Research Ethics Committee B (HREC/2022/MNHB/87668). Recognition of prior ethics approval was received through the Australian National University Human Research Ethics Committee. Approval from Queensland Health Communicable Diseases Branch Data Custodian was also sought for the study.

3. Results

3.1. VZV notifications and demographic distribution

A total of 87,929 cases of VZV were notified in Queensland from 01 January 2010 to 31 December 2021. After exclusion of probable cases ($n=38$) and cases of unknown sex and/or age ($n=132$), 87,759 cases were available for analysis. A majority of the cases ($n=61,298$, 70%) had a final designation of unspecified followed by shingles ($n=19,927$, 23%) and chickenpox ($n=6,534$, 7%) (Figure 3, Appendix Table 2). The VZV notification rate increased by 99% from 99.1 per 100,000 population per year (95% CI 96.2–102.1) in 2010 to 197.5 per 100,000 population per year (95% CI 193.6–201.0) in 2021 (Figure 4).

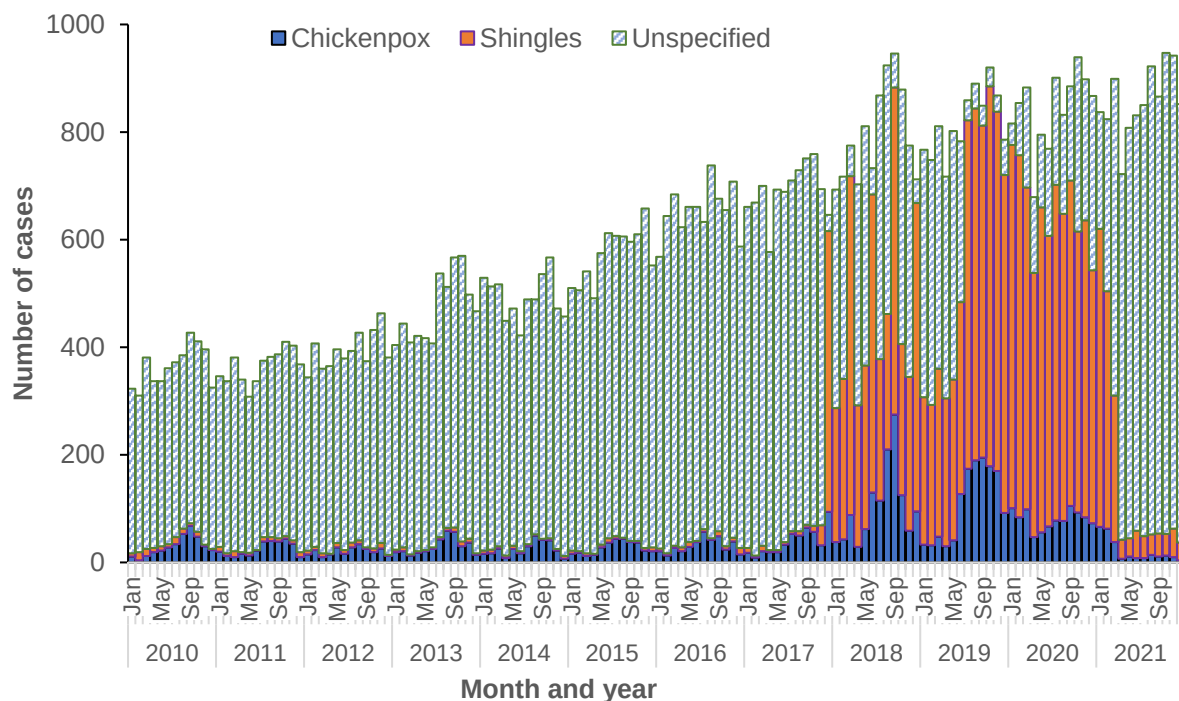


Figure 3. VZV notifications by month and year and clinical presentation, Queensland, 2010–2021

The overall proportion of cases among females (55%) was higher than the males (45%) over the years 2010–2021, with similar proportions each year (Appendix Table 1, Figure 4). The notification rate for females increased by 102% from 106.1 per 100,000 population per year (95% CI 101.9–110.5) in 2010 to 214.3 per 100,000 population per year (95% CI 208.8–220.0) in 2021 and for males by 96% from 92.1 (95% CI 88.2–96.2) to 180.2 (95% CI 175.1–185.4) per 100,000 population per year in 2010 and 2021, respectively (Figure 4).

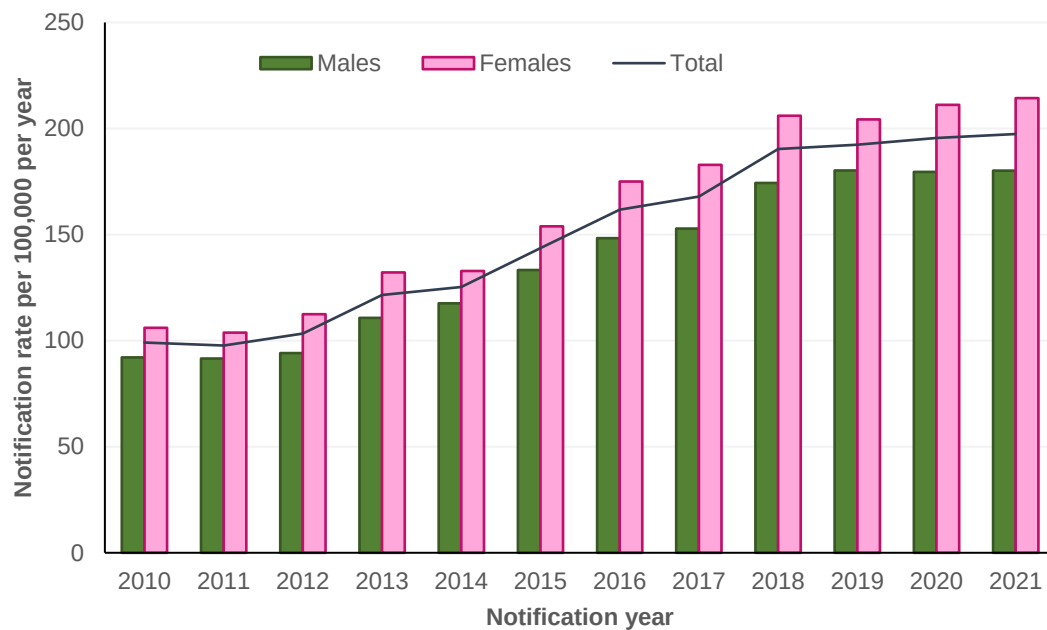
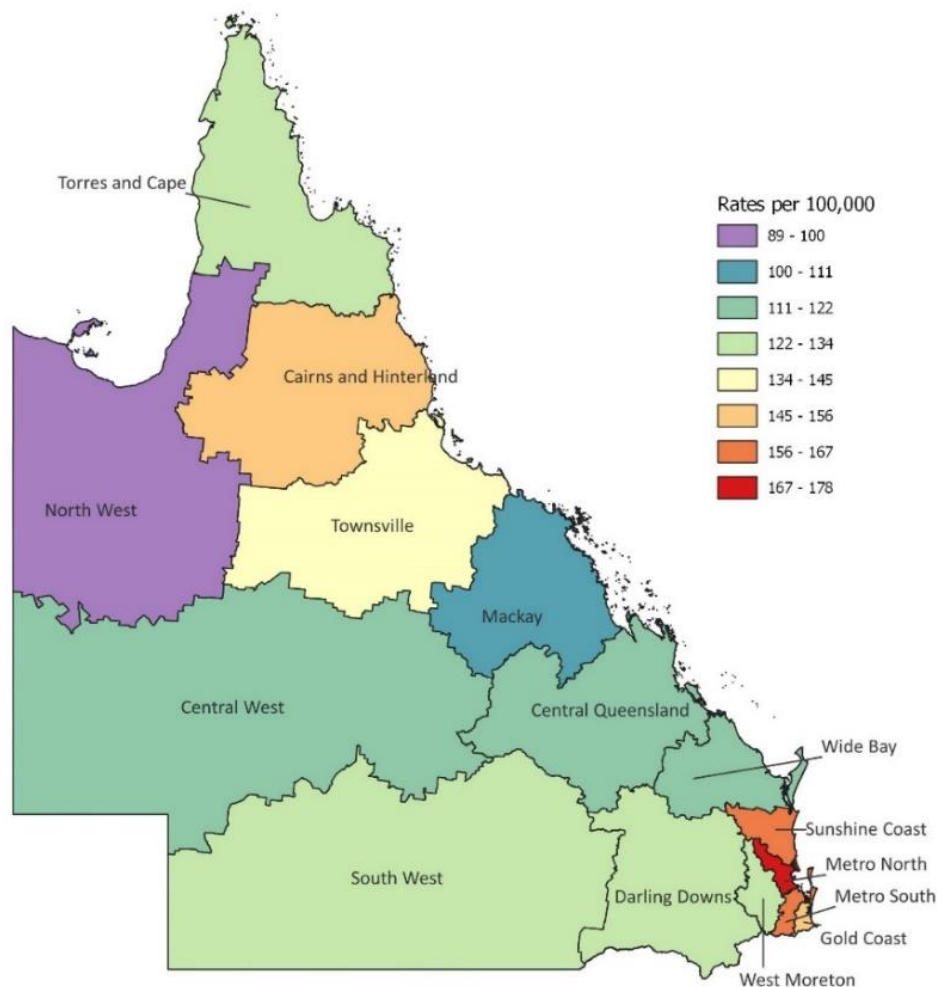


Figure 4. VZV notification rates per 100,000 population per year by sex and year, Queensland, 2010–2021

A majority of the cases were reported from Metro South (25%) followed by Metro North (24%) and Gold Coast (12%) HHSs. The rate of notification was highest in Metro North (178 per 100,000 per year, 95% CI 175.6–180.4), Metro South (166 per 100,000 per year, 95% CI 163.5–167.8) and Sunshine Coast (162 per 100,000 per year, 95% CI 158.2–165.4) (Figure 5).



* 56 cases with unassigned Hospital and Health Services excluded

Figure 5. VZV notification rates by Hospital and Health Services, Queensland, 2010–2021

3.2. Chickenpox and shingles clinical presentations with enhanced surveillance

There were 32,660 VZV notifications from December 2017 to March 2021 and the clinical presentation was known for 70% (22,779/32,660). Among these cases, the proportion of VZV notifications identified as chickenpox was highest among infants <1 years of age (97%) which decreased with increasing age. The proportion of shingles notifications increased with increasing age and included more than 98% of the cases in those 60 years and older (Figure 6). The year of age with approximately equal proportions of notifications from chickenpox and shingles was 15 years. A total of 9,881 cases with unspecified clinical presentation was excluded from further outcome specific analyses.

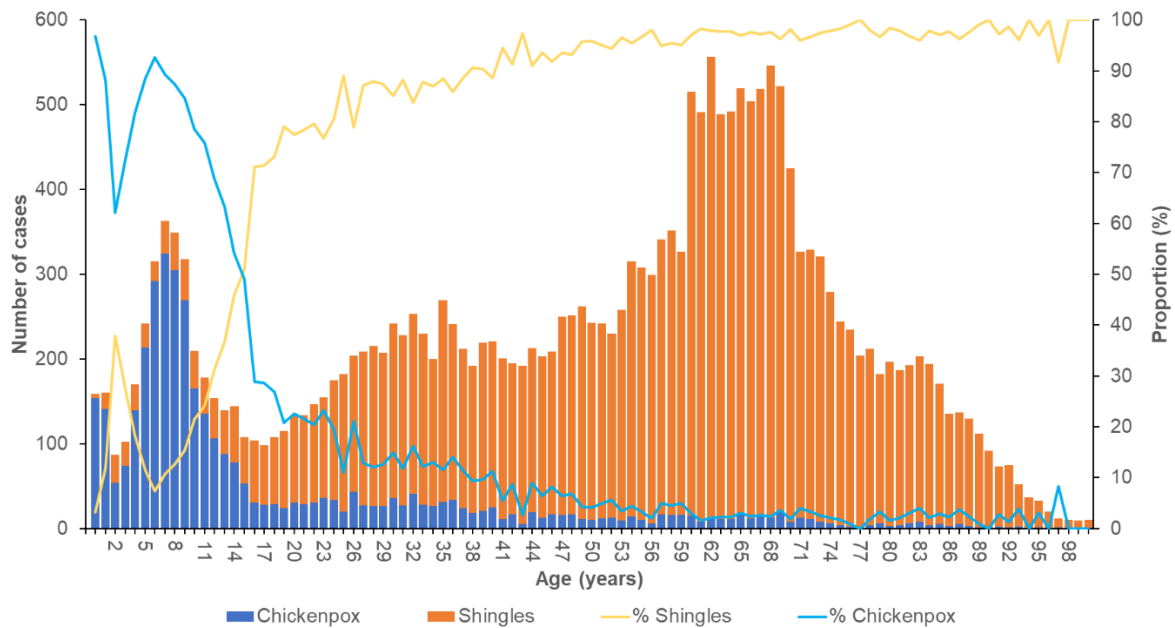


Figure 6. VZV notifications by age and clinical presentation for notifications where clinical presentation was known, Queensland, December 2017–March 2021

The overall proportion of unspecified clinical presentation decreased from 70% for 2010–2021 to 15% for the intermittent enhanced surveillance periods — 01 December 2017 to 30 September 2018 (December 2017, March 2018, June 2018, and September 2018) and 01 August 2019 to 31 December 2020. The proportion of unspecified clinical presentation was 8–22% among different ages for these follow-up periods (Figure 7).

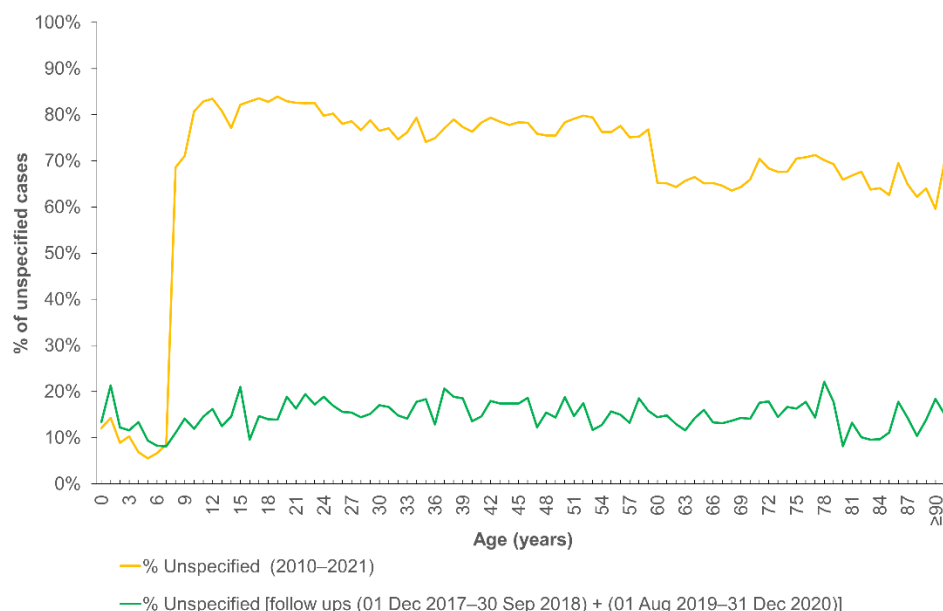


Figure 7. Proportion of unspecified cases among all notified cases by age and specific period

Intermittent enhanced surveillance to determine clinical presentation for cases of all age groups from 01 August 2019–31 December 2020 (n=17,086) showed that the rate of chickenpox presentation was 78 per 100,000 per year among infants <1 years of age compared to 41 per 100,000 per year among 1–2 years (Figure 8). The rate of shingles notification increased with age but was lower for 70–79 years (224 per 100,000 per year) compared to 60–69 years (274 per 100,000 per year) (Figure 8). A total of 4,899 (28%) cases with unspecified clinical presentation was excluded from the analysis.

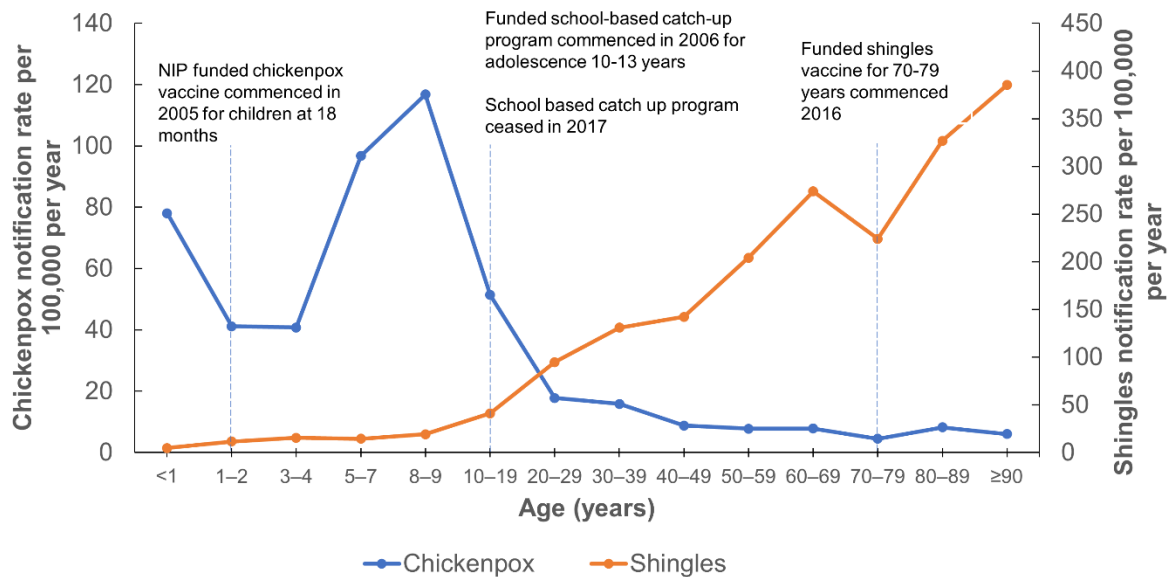


Figure 8. VZV notification rates by clinical presentation (based on enhanced surveillance) and age groups, Queensland, 01 August 2019–31 December 2020

Clinical presentation among children <8 years old from 2010–2021 showed the chickenpox notification rate plateaued at 12 months of age and fell sharply at 18 months of age (eligible for chickenpox vaccine) and then gradually increased with increasing age. The rate was 48% higher among children 12–17 months of age but 36% lower among 18–23 months compared to <12 months for the period 2010–2021 (Figure 9). Cases with unspecified clinical presentation (n=443, 9%) were excluded from the analysis.

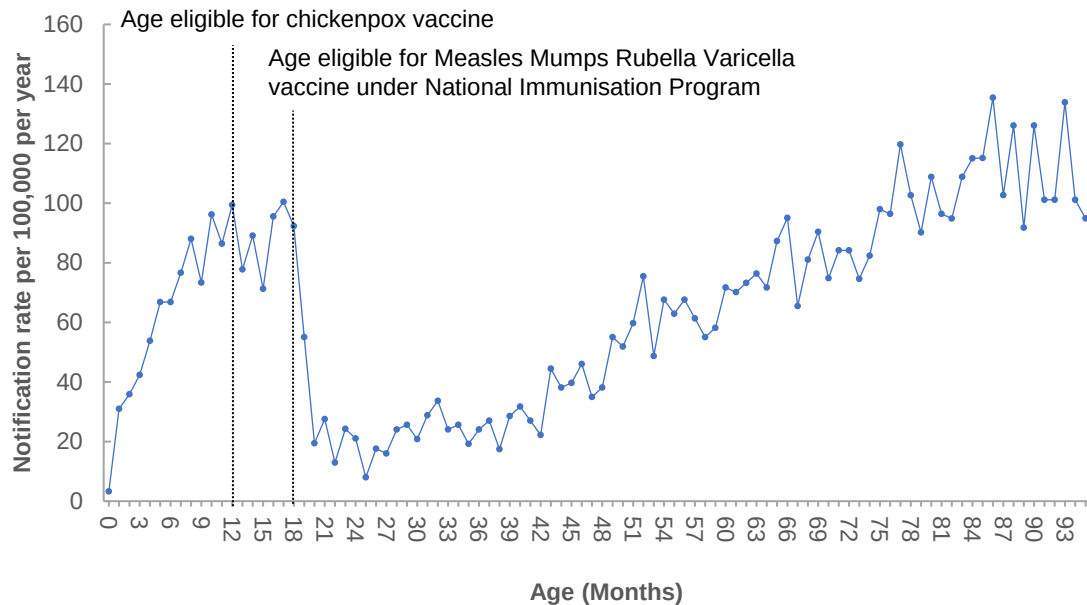


Figure 9. Chickenpox notification rates (based on enhanced surveillance) among children of <8 years of age, Queensland, 2010–2021

All the cases aged 60 years and older were assumed as shingles for this analysis. A decreasing trend in notification was observed for the age group 70–79 years for each year after vaccine introduction (2016) (Figure 10). This can be observed for 2018 and 2021 compared to the years 2010, 2012, and 2015 (prior to the shingles vaccination program) (Figure 10).

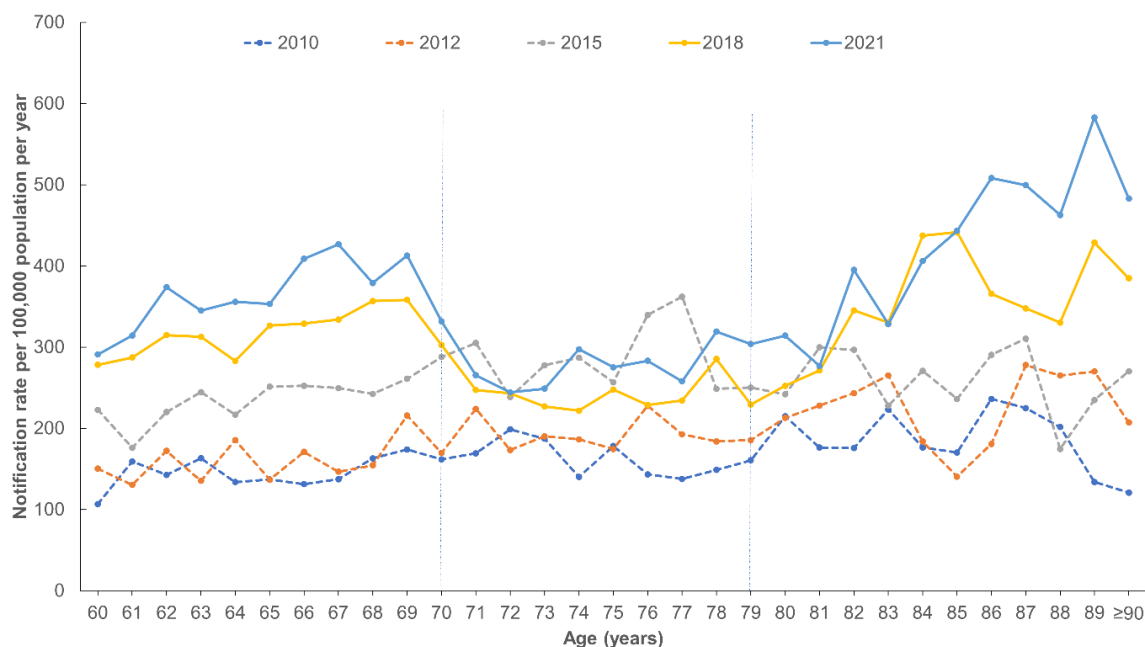


Figure 10. Shingles notification rates per 100,000 per year by age and selected years, Queensland (assuming all cases aged 60 years and above were shingles)

Notification rates of shingles decreased by 12–22% among 70–79 years old over the years 2017–2021 relative to the same age group in 2016 (Figure 11). However, the rate increased among younger (60–69) and older (≥ 85) age groups (ineligible to receive shingles vaccine) with a small decline among historically eligible cohort (previously eligible, but not eligible in the specific year) of 80–84 years of age (2017–2018).

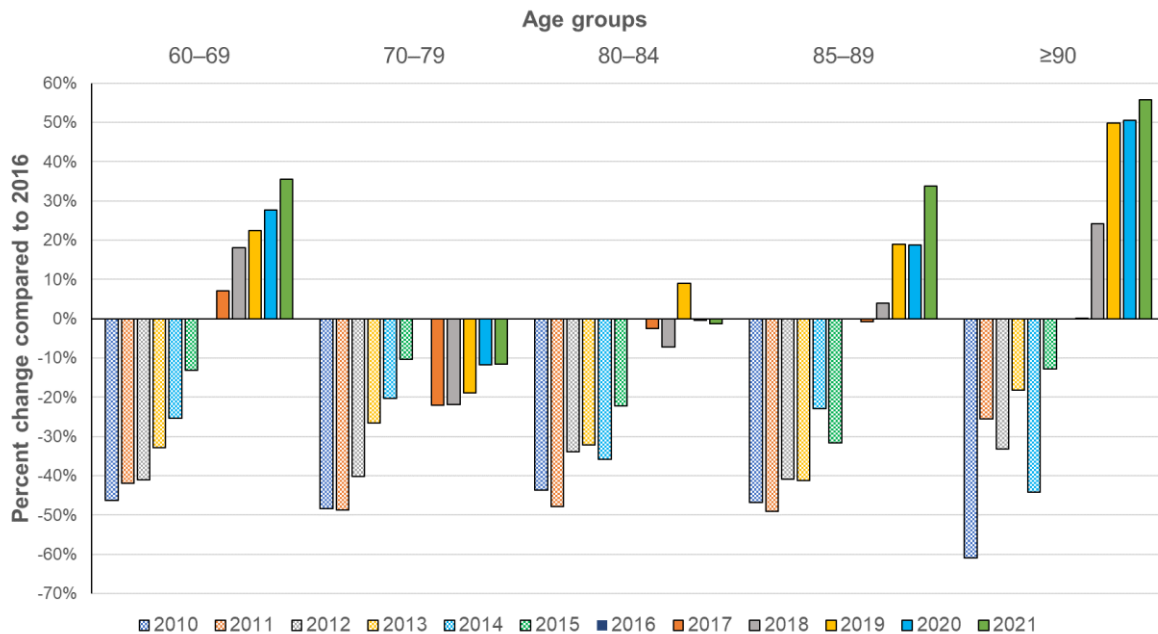


Figure 11. Percent change in notification rate of shingles for each age group by year, compared to 2016, Queensland (assuming all cases aged 60 years and above were shingles)

An increasing trend of shingles was observed over the years 2010–2016 (before shingles vaccine was available under the Shingles Vaccination Program, 01 November 2016) among individuals aged 60 years and older (Figure 12). A comparison of shingles cases since 2017 showed a steady increasing trend among those too old for vaccination when the program started (born on or before 01 November 1936) and cohorts too young to be eligible (aged 60–69 years) to receive shingles vaccines under the program. Notification rates were lower among the cohort who were currently eligible to receive shingles vaccine (70–79 years of age) in the specific year, followed by an historically eligible cohort (previously eligible, but not eligible in the specific year; 80 years and above and born on or after 02 November 1936). The notification rate of shingles for those over the age of 60 years increased by 89% from 2010–2016 compared to 13% for 70–79 years of age from 2017–2021 (Figure 12).

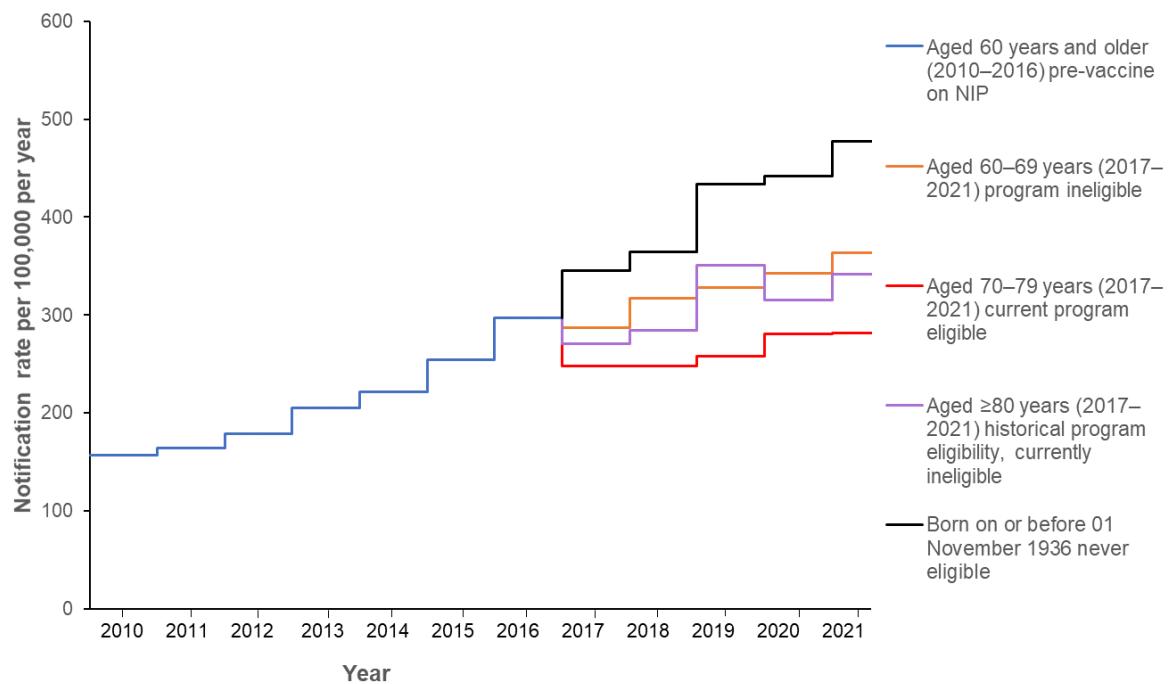


Figure 12. Shingles notification rates per 100,000 per year by year and birth cohort based on availability of shingles vaccines under NIP, Queensland (assuming all cases aged 60 years and above were shingles)

3.3. Clinical presentation and hospitalisation

Of the total cases, 2% (1,672) were known to be hospitalised, 19% (16,871) not hospitalised and status for 79% (69,216) were unknown (Appendix Table 2). The hospitalisation data were used to identify clinical presentation and 15% (244/1,672) were associated with chickenpox, 83% (1,396/1,672) with shingles and 2% (32/1,672) with unspecified clinical presentation. Hospitalisation data were available for 2015 onwards and for specific age groups at other times, depending on the enhanced surveillance period. During 01 August 2019–31 December 2020, cases of all age groups were followed up and data on hospitalisation status for 68% (9,818/14,331) of the cases were available. Of the cases hospitalised during the period, 11% (93/815) were identified with chickenpox, 86% (697/815) with shingles and 3% (25/815) with unspecified clinical presentation.

The hospitalisation rate for chickenpox was highest (6.7 per 100,000 population per year, 95% CI 2.5–17.9) among children of <1 years of age (ineligible for chickenpox vaccine) (Figure 13). Whereas the hospitalisation rate for shingles was highest among older population of ≥80 years (ineligible for funded shingles vaccine) compared to younger age groups. The overall hospitalisation rate was higher among shingles cases (13.5 per 100,000 per year, 95% CI

12.5–14.5) compared to chickenpox cases (1.8 per 100,000 per year, 95% CI 1.5–2.2). Cases with unspecified clinical presentation (n=25, 3%) were excluded from the analysis.

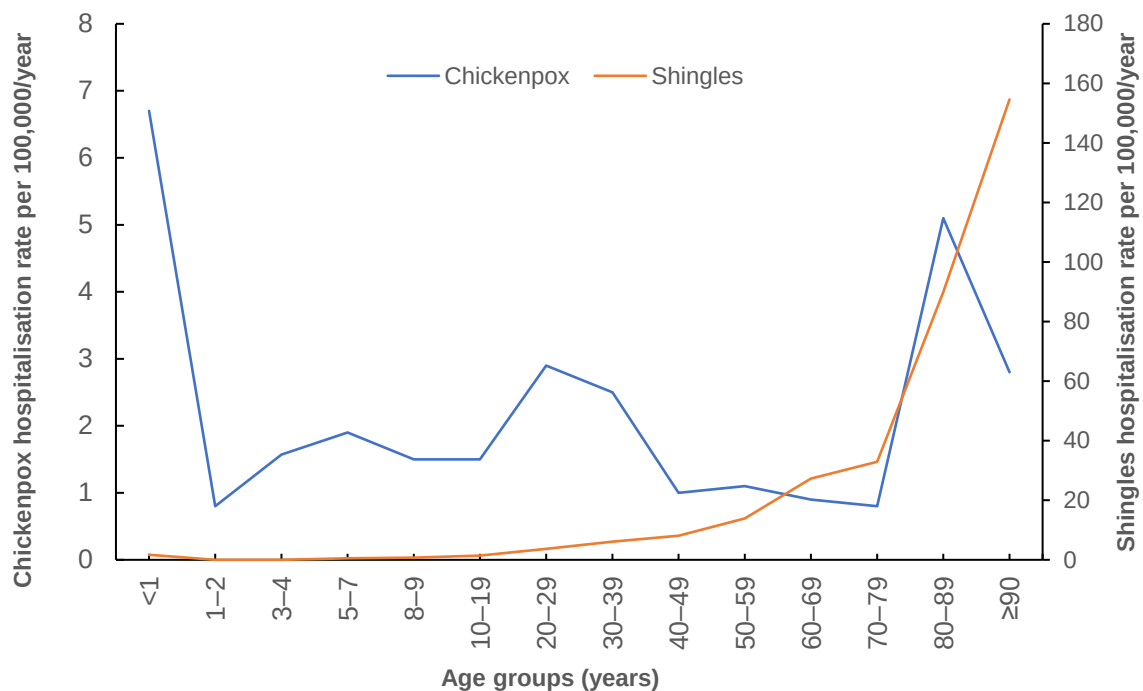


Figure 13. VZV hospitalisation rates by age group and specific clinical presentation, Queensland, 01 August 2019–31 December 2020

3.4. VZV infection and Indigenous Australians

Indigenous Australian status was known for 98% of the cases notified between 2018–2020 and were analysed further. The rate of notification of VZV during the period was highest among non-Indigenous Australian population (189.5 per 100,000 per year, 95% CI 187.2–191.7) compared to the Indigenous Australian population (139.3 per 100,000 per year, 95% CI 130.8–148.2). However, the notification rate was higher among Indigenous Australian population of ≥70 years old (353.8 per 100,000 per year, 95% CI 276.4–452.9) compared to non-Indigenous population (299 per 100,000 per year, 95% CI 290.8–307.5). Based on the specific clinical presentation, IRR of chickenpox among Indigenous Australians was 1.3 (95% CI 1.1–1.5) for all age groups compared to non-Indigenous Australians, whereas shingles was higher among non-Indigenous Australians (IRR: 1.7, 95% CI 1.5–1.8).

3.5. Seasonality

Seasonality of VZV infection was analysed for children <8 years of age and pooled data for 2010–2020 showed that chickenpox notifications peaked in August (Figure 14). The Edward's model also indicated that a significant peak in the number of cases was expected during

August based on the observed seasonal pattern in the data (Chi square goodness of fit test significant, $p < 0.001$). Peaks were observed for pooled data in March and October for shingles among the same population group and study period, but the seasonality pattern was not significant by the test model (Figure 15).

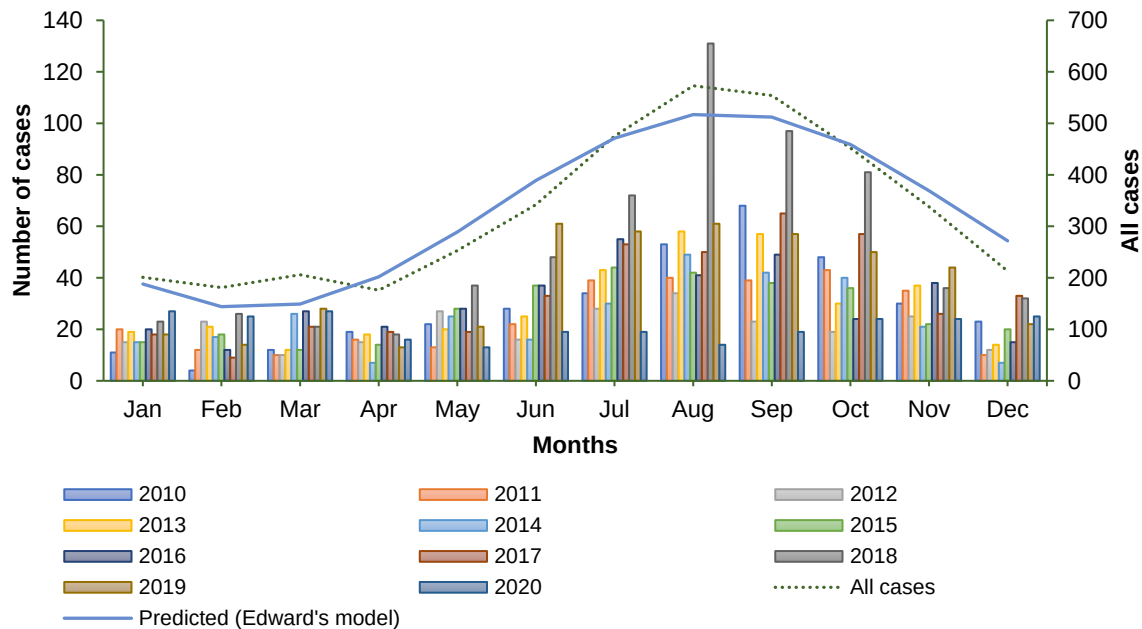


Figure 14. Chickenpox cases among children <8 years of age by months and years of notification, Queensland, 2010–2020

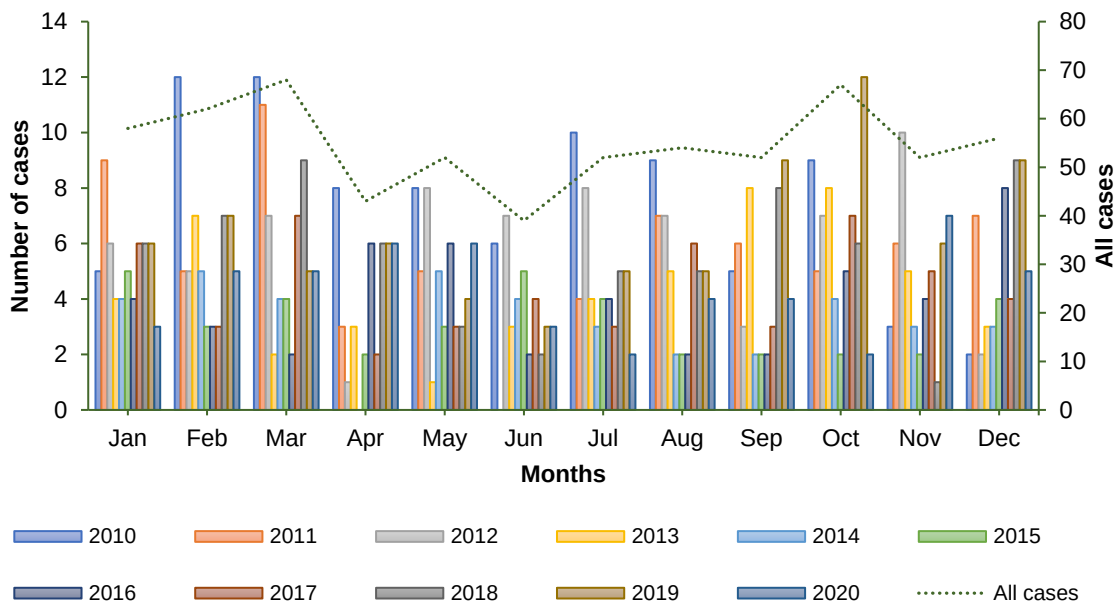


Figure 15. Shingles among children <8 years of age by months and years of notification, Queensland, 2010–2020

3.6. Trend

The distribution of data based on age group, sex, and year indicated dispersion of data and negative binomial regression model was suitable for the analysis. There was a significant increase in the VZV notification rate observed over the years 2010–2021, after adjusting for age and sex ($p<0.001$) (Table 3). The percent change in rate was estimated to be an increase of 5.7% (95% CI 4.9–6.4) each year, holding other variables constant (non-adjusted percent change in rate 5.9%, IRR: 1.06, 95% CI 1.04–1.08). The notification rate increased with increasing age and was 3.4 (95% CI 2.9–3.9) times higher among cases ≥ 70 years of age, and 2.9 (95% CI 2.5–3.3) times higher among cases ≥ 50 years of age, compared to infants aged <1 year. The rate among females was 1.08 times higher compared to males (IRR=1.1, $p<0.001$).

Table 3. Incidence rate ratio of VZV notifications in Queensland, adjusted by age and sex over the years 2010–2021*

Characteristics	IRR**	P- value	95% CI	
Year***	1.06	<0.001	1.05	1.06
Age group				
<1	Reference			
1–2	0.72	<0.001	0.61	0.83
3–4	0.82	<0.001	0.71	0.96
5–7	1.65	<0.001	1.43	1.90
8–9	1.97	<0.001	1.71	2.27
10–19	1.39	<0.001	1.21	1.60
20–29	1.44	<0.001	1.26	1.65
30–39	1.58	<0.001	1.38	1.82
40–49	1.61	<0.001	1.40	1.85
50–59	2.28	<0.001	1.98	2.61
60–69	3.17	<0.001	2.77	3.64
≥ 70	3.42	<0.001	2.98	3.93
Sex				
Male	Reference			
Female	1.08	<0.001	1.02	1.13

* Analysis by negative binomial regression model including age, sex, and year variables

** IRR: Incidence rate ratio or rate ratio

***Year categorised as a continuous variable before analysis

4. Discussion

The VZV notification rate has increased over the years 2010–2021 in Queensland. As with other notifiable diseases, the increasing trend can be due to true increase in incidence of VZV, increase in testing requested by diagnosing clinicians, changes in laboratory testing practices, or changes in the underlying age structure of the population. The risk of shingles increases

with age and the increase in ageing population globally (28), and it has been reported that the funded chickenpox vaccine in Australia has led to a decline in chickenpox notifications, hospitalisations, and deaths (29). The increase in overall trend for VZV notification was higher among ≥ 50 years old, who are at highest risk of shingles. Hence, the burden of VZV is likely to be due to an actual increase in shingles cases. A higher notification rate of VZV infection was observed among females compared to males as reported by others (30, 31), likely to be due to differences in health seeking behaviours. Although the overall notification rate of VZV was higher among non-Indigenous Australians compared to Indigenous Australians, the rate of chickenpox was higher among Indigenous Australians. A previous study has reported higher chickenpox hospitalisation rate for Indigenous Australians (32). A majority of chickenpox cases among children < 8 years of age occurred in August, a similar seasonal pattern reported by a study in Western Australia among population of all ages (33). Hence, the trend and pattern of VZV infections in Queensland is similar to reported elsewhere in Australia.

Our use of enhanced surveillance data allowed us to demonstrate age-specific impacts in cohorts eligible for vaccination. In the absence of clinical presentation data, it is challenging to determine the burden of the specific diseases and understand the impact of disease-specific vaccination programs. A routine age-group specific and targeted, intermittent enhanced surveillance for clinical presentation is useful to understand vaccine impact, make future recommendations and plan further time limited enhanced surveillance with optimal utilisation of available resources.

A single dose of funded chickenpox vaccine is made available at the age of 18 months which corresponds to the decreased incidence rate for children 2 years of age. The immunity due to vaccine wanes with age as observed with increase in notification rate among 5–9-year-olds. It is consistent with the previous reports of higher notification rate among the age group in Australia (34-36). Additionally, in temperate climates, the varicella attack rate is known to be highest among pre-school children (1–4 years) or early primary school (5–9 years), which results in more than 90% of people being infected before adolescence (1). As the data were available for notifications after the introduction of chickenpox vaccine under NIP, impact of the vaccination program could not be determined in the absence of pre-vaccine notification data. However, the impact of chickenpox vaccine is seen with plateauing of number of cases after 12 months (age eligible for vaccination), a sharp decline from 18 months (NIP schedule for MMRV vaccine), and a higher hospitalisation rate among children < 1 year of age.

The VZV notification rate increased with an increase in age among those aged 50 years and older. The rate of shingles notification declined among 70–79 years of age from 2017 after the shingles vaccine was available for the age group under NIP in November 2016. Whilst difficult

to assign causality using case series data, there are some elements of our analysis that suggest a likely vaccine impact. The lowest notification rate was among the specific age cohort eligible to receive the vaccine under the program. The rate increased after 79 years of age which is likely to be due to waning immunity with age. The hospitalisation rate for shingles increased with increasing age, similar to a previous study which showed increasing hospitalisation rates with age among Australians (32). The increase in hospitalisation rate by 173% among 80–89 years of age compared to 70–79 years but only 21% among 70–79 years compared to 60–69 years indicated possible impact of vaccination program on the severity outcome of shingles.

Although a single dose of chickenpox vaccine has been shown to be effective in preventing hospitalisation, it is known to be moderately effective in preventing chickenpox with declining effectiveness over time (8, 37, 38). The effectiveness has been shown to decline by 34%, from 93% to 61%, three years after vaccination (38). Two-dose chickenpox vaccination strategy is considered more effective to prevent transmission and breakthrough chickenpox (39). As per the Australian Immunisation Handbook, a second dose of chickenpox vaccine is recommended for children <14 years old (≥ 4 weeks after first dose) (5). Therefore, introduction of second dose in the NIP should be considered to improve vaccine uptake and impact. A routine two dose chickenpox vaccine schedule in the United States (US) includes a first dose given at 12–15 months of age and a second dose at 4–6 years (40). A study in the US estimated 90–95% decline in incidence of chickenpox among 5–19 years of age after two doses of varicella vaccine were introduced compared to pre-vaccine period (41). The risk of developing breakthrough chickenpox has been determined to be 3.3 folds lower among two doses vaccine recipients compared to a single dose recipients (42). Two doses vaccine are recommended in the prevention of transmission and control of chickenpox outbreaks (43). The future vaccination option against chickenpox may include first dose of monovalent chickenpox vaccine at 12 months with MMRV vaccine at 18 months. The combination MMRV vaccine is not recommended at 12 months due to an increased risk of adverse events (fever, febrile seizures) when compared to administration of monovalent chickenpox vaccine and MMR (5). A second dose of a monovalent vaccine could be considered in the NIP at the 4-year-old time point, prior to increasing rates of chickenpox in early primary school years.

The efficacy of current single dose live-attenuated shingles vaccine made available under shingles vaccination program is reported to be 70% against incidence of shingles among 50–59 years old (44). It is recommended only for immunocompetent adults of ≥ 50 years old (45). The efficacy decreases against post-herpetic neuralgia, a pain side effect of shingles, and among ≥ 80 years old (45). Effectiveness of the vaccine against incidence of shingles has also been shown to decline significantly by 30–65% in 5–10 years after vaccination (46–48). A

recombinant adjuvanted shingles vaccine (two dose schedule given 2–6 months apart in immunocompetent individuals or 1–2 months apart in immunocompromised individuals) is registered for use in Australia for adults aged 18–49 years at increased risk of shingles and all adults aged ≥ 50 years (49). The recombinant vaccine has been funded for Aboriginal and Torres Strait Islander people aged ≥ 50 years, non-Indigenous people aged ≥ 65 years, and certain immunocompromised people aged ≥ 18 years since 1 November 2023 (49, 50). The vaccine has efficacy of 90% in immunocompetent adults ≥ 70 years (51), can last up to 7 years and may provide protection at least 10 years after vaccination (47, 52, 53).

Passive surveillance of diseases such as VZV infections through notifications by pathology laboratories provides limited data. Information on clinical presentation and vaccination status of the notified cases are not currently routinely available unless followed by enhanced surveillance after notifications or data linkage. Prospects of data linkage have improved with jurisdictions now having access to the Australian Immunisation Register data. Using surveillance data has limitations. Although a very high proportion of cases were unspecified for the study period (2010–2021), the targeted follow-ups reduced the proportion to 8–12%. This was useful to analyse the data by clinical presentation among specific age groups for the follow up periods. Assumption and exclusion of cases with unknown clinical presentation were required for meaningful analyses. Surveillance data are also subject to selection bias due to differences in health seeking behaviour or access to health care facilities of individuals. There are also no guidelines for medical practitioners to request a VZV test and only cases recommended for testing are notified. Therefore, estimates of the disease burden based on laboratory notifications is likely to be a substantial underestimate of true disease burden. There is also a possibility of selection bias with the analysis of variables with missing or incomplete data, however data quality is likely to be stable over study period.

During 2020–2021, the COVID-19 pandemic may have had impact on varicella-zoster notifications and vaccine coverage due to changes in laboratory testing priorities; resource allocation for pandemic management; access to health care facilities, and changes in health-seeking behaviours. In Queensland, single dose varicella vaccine coverage remained high ($>90\%$) for children during the pandemic (54). In 2021, coverage of shingles vaccine in Queensland among those aged 70– <71 and 71–79 years remained modest at 40.9% and 55.3%, respectively (55). Coverage of shingles vaccine among those aged 70– <71 years was 44.9% in 2019 and 46.2% in 2020 (56). There is scope for an increase in vaccine coverage to further improve disease control.

Although a case series study does not have a formal control group for comparison, making causal inference difficult, it is useful to determine trends of the disease and impact of vaccine

interventions as demonstrated by the decrease in notification of shingles after the introduction of shingles vaccination program. Likewise, a sharp decline in chickenpox notifications at 18 months and known effectiveness of chickenpox vaccines indicate the impact of vaccination program. To improve our understanding of VZV epidemiology in Queensland, it would be useful to conduct further analysis of data with vaccination status known at the individual level; understand protective effect of two doses of chickenpox vaccine; analyse data based on date of vaccination and disease outcome; chickenpox and shingles vaccines uptake and coverage, as well as effectiveness of the available vaccines in preventing hospitalisation outcome.

5. Conclusion

Using laboratory derived surveillance data and intermittent enhanced surveillance, we were able to draw inferences about impact of a vaccination program in conjunction with time and age-related case and rate assessment. A complete and continuous enhanced surveillance data are preferable, but intermittent high-quality surveillance may be adequate to answer focussed questions on age-group specific rates of infection and on vaccine impact. Although the incidence of VZV infections has increased in Queensland, the availability of vaccines for chickenpox and shingles have had an impact on notification epidemiology. Appropriate vaccination strategies including expanding to two doses of chickenpox vaccine for children and moving to the adjuvanted recombinant shingles vaccine, potentially across a broader age range, should be considered to further reduce the burden of VZV infection.

6. References

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7. Appendix

Table 1. Demographic characteristics of notified cases of varicella-zoster, Queensland, 2010–2021

Characteristics	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Five year mean (2016– 2020)
Cases (n)	4,365	4,374	4,721	5,653	5,912	6,864	7,838	8,278	9,536	9,800	10,118	9,114	10,300
% Of total (n=87,759)	5.0	5.0	5.4	6.4	6.7	7.8	8.9	9.4	10.9	11.2	11.5	11.7	11.7
Sex													
Male (n)	2,026	2,046	2,145	2,568	2,763	3,165	3,564	3,736	4,329	4,550	4,603	4,156	4,660
%	46.4	46.8	45.4	45.4	46.7	46.1	45.5	45.1	45.4	46.4	45.5	45.6	45.2
Female (n)	2,339	2,328	2,576	3,085	3,149	3,699	4,274	4,542	5,207	5,250	5,515	4,958	5,640
%	53.6	53.2	54.6	54.6	53.3	53.9	54.5	54.9	54.6	53.6	54.5	54.4	54.8
Age groups (years)													
<1	43	48	32	47	38	49	33	44	63	57	47	49	53
%	1.0	1.1	0.7	0.8	0.6	0.7	0.4	0.5	0.7	0.6	0.5	0.5	0.5
1–2	52	45	53	67	50	54	63	96	98	99	68	85	69
%	1.2	1.0	1.1	1.2	0.9	0.8	0.8	1.2	1.0	1.0	0.7	0.9	0.7
3–4	107	77	51	75	53	68	93	83	111	83	80	90	52
%	2.5	1.8	1.1	1.3	0.9	1.0	1.2	1.0	1.2	0.9	0.8	1	0.5
5–7	248	205	188	232	198	193	227	241	431	307	195	280	155
%	5.7	4.7	4.0	4.1	3.4	2.8	2.9	2.9	4.5	3.1	1.9	3.1	1.5

Characteristics	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Five year mean (2016– 2020)	2021
8–9	192	146	145	196	174	183	157	199	284	262	158	212	155
%	4.4	3.3	3.1	3.5	2.9	2.7	2.0	2.4	3.0	2.7	1.6	2.3	1.5
10–19	553	551	534	647	592	700	645	656	828	775	654	712	634
%	12.7	12.6	11.3	11.5	10.0	10.2	8.2	7.9	8.7	7.9	6.5	7.8	6.2
20–29	444	474	537	617	670	749	824	915	954	978	992	933	984
%	10.2	10.8	11.4	10.9	11.3	10.9	10.5	11.1	10.0	10.0	9.8	10.2	9.6
30–39	446	427	479	567	629	690	872	965	1118	1211	1297	1093	1343
%	10.2	9.8	10.2	10.0	10.6	10.1	11.1	11.7	11.7	12.4	12.8	12.0	13.0
40–49	458	429	532	621	609	767	861	952	1082	1121	1264	1056	1264
%	10.5	9.8	11.3	11.0	10.3	11.2	11.0	11.5	11.4	11.4	12.5	11.6	12.3
50–59	572	619	644	775	874	1018	1171	1272	1443	1467	1661	1403	1598
%	13.1	14.2	13.6	13.7	14.8	14.8	14.9	15.4	15.1	15.0	16.4	15.4	15.5
60–69	605	679	713	839	958	1139	1344	1459	1642	1743	1870	1612	2035
%	13.9	15.5	15.1	14.8	16.2	16.6	17.2	17.6	17.2	17.8	18.5	17.7	19.8
≥70	645	674	813	970	1067	1254	1548	1396	1482	1697	1832	1591	1958
%	14.8	15.4	17.2	17.2	18.1	18.3	19.8	16.9	15.5	17.3	18.1	17.5	19.0
Aboriginal and Torres Strait Islander Status													
Non-Indigenous	2,377	2,391	2,642	3,204	3,361	3,903	4,643	5,705	8,928	9,213	9,467	7,591	7,416
%	54.5	54.7	56.0	56.7	56.9	56.9	59.2	68.9	93.6	94.0	93.6	83.3	72

Characteristics	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Five year mean (2016– 2020)	2021
Aboriginal and/or Torres Strait Islander	189	161	163	191	220	198	234	252	305	355	328	295	252
%	4.3	3.7	3.5	3.4	3.7	2.9	3.0	3.0	3.2	3.6	3.2	3.2	2.5
Unknown	1,799	1,822	1,916	2,258	2,331	2,763	2,961	2,321	303	232	323	1,228	2,632
%	41.2	41.7	40.6	39.9	39.4	40.3	37.8	28.0	3.2	2.4	3.2	0.1	25.6

Table 2. Clinical presentation, hospital outcome and vaccination status of Varicella zoster, Queensland, 2010–2021

Characteristics	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Five year mean (2016– 2020)	2021
Clinical presentation													
Varicella	352	300	251	357	301	331	375	470	1,269	1,311	964	878	253
%	8.1	6.9	5.3	6.3	5.1	4.8	4.8	5.7	13.3	13.4	9.5	9.3	2.5
Herpes Zoster	98	75	74	58	52	53	73	624	4,561	5,699	6,925	3576	1,635
%	2.3	1.7	1.6	1.0	0.9	0.8	0.9	7.5	47.8	58.2	68.4	36.6	15.9
Unspecified	3,915	3,999	4,396	5,238	5,559	6,480	7,390	7,184	3,706	2,790	2,229	4659.8	8,412
%	89.7	91.4	93.1	92.7	94.0	94.4	94.3	86.8	38.9	28.5	22.0	54.1	81.7
Hospitalisation													
Yes	0	0	0	0	0	11	10	26	320	363	649	274	293

Characteristics	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Five year mean (2016– 2020)	2021
%	0	0	0	0	0	0.16	0.13	0.31	3.36	3.7	6.41	2.8	2.84
No	0	0	0	0	0	339	401	789	3,254	4,787	5,970	3040	1,331
%	0	0	0	0	0	4.94	5.12	9.53	34.12	48.85	59	31.3	12.92
Unknown	4,365	4,374	4,721	5,653	5,912	6,514	7,427	7,463	5,962	4,650	3,499	5800	8,676
%	100	100	100	100	100	94.9	94.8	90.2	62.5	47.5	34.6	65.9	84.2
Vaccination status													
Vaccinated*	244	251	284	431	425	540	635	851	1,580	1,425	1,285	1,155	1,096
%	5.6	5.7	6.0	7.6	7.2	7.9	8.1	10.3	16.6	14.5	12.7	12.4	10.6
Unvaccinated	227	225	108	95	110	120	102	288	1,143	2,682	1,618	1,167	1,471
%	5.2	5.1	2.3	1.7	1.9	1.8	1.3	3.5	12.0	27.4	16.0	12.0	14.3
Unknown	3,894	3,898	4,329	5,127	5,377	6,204	7,101	7,139	6,813	5,693	7,215	6,792	7,733
%	89.2	89.1	91.7	90.7	91.0	90.4	90.6	86.2	71.5	58.1	71.3	75.5	75.1

*Vaccinated: Received varicella, zoster or MMRV vaccines (one or more number of doses)

Chapter III:

Investigation of an acute public health problem or threat

Part A

An investigation of Shiga toxin-producing *Escherichia coli* notifications in Queensland, 2020–2022

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Prologue

On 24 June 2022, a discussion on the increase in notifications of Shiga toxin producing *Escherichia coli* (STEC) cases was initiated by the Metro South Public Health Unit, Queensland Health. This was after the unit followed up an STEC notification from a test initially requested by a naturopath. OzFoodNet Queensland initiated further investigation of all cases notified through this pathway since 2020. A retrospective review of all STEC cases notified in Queensland from 2020–2022 was conducted to understand the significance of cases diagnosed by alternative health practitioners.

My role

After discussion with my supervisors and OzFoodNet Queensland, this project was identified as a suitable project for further investigation of an acute public health problem. It was aimed to contribute to the review of STEC guidelines in Queensland. I took on the role of an investigator from conducting a detailed epidemiological review to preparation of a report for dissemination. I was involved in collation of information on case demographic characteristics and clinical presentation collected by public health units. Laboratory test results were obtained from pathology laboratories. I conducted a literature review as relevant to the project, analysed the data, and drafted a report. The findings were shared with Queensland Health STEC Guidelines Working Group including public health physicians from public health units, scientists from pathology laboratories, and OzFoodNet epidemiologists in Queensland. After completion of this investigation, I presented findings to Communicable Disease Control team at the Metro South Public Health Unit and at the OzFoodNet face to face meeting held in Brisbane. I also submitted a manuscript as a Research Letter to the journal *Emerging Infectious Diseases* and responded to reviewer's comments.

Lessons learned

The project provided an opportunity to understand the significance of disease surveillance in identifying an acute public health problem. While drafting the report, I learned that surveillance data are subject to change with the availability of additional information from cases and pathology laboratories over time. Hence, a situation report or epidemiological snapshot may require further analyses and needs to be updated before dissemination. There is likely to be recall errors in information obtained from cases and this could be minimised by conducting interviews as early as cases are identified. An understanding of pathology laboratory tests performed for a specific condition is also important to allow for the best analysis and interpretation of findings.

Public health impact

This Chapter highlighted the impact changes in routine laboratory testing practices can have on the nature of cases and the trend of a notifiable condition. The new notification pathway and an increase in asymptomatic or pauci-symptomatic clinical presentation of cases demonstrated that true incidence of a disease based on notification data may be an underestimate. Management of all notified cases may not be feasible in terms of resources available. Therefore, guidelines for the management of a notifiable condition need to consider factors such as severity, outcome, transmission, and laboratory test results. Disease surveillance is important not only to monitor and identify a public health problem but also to provide recommendations to manage the problem.

Acknowledgements

I thank OzFoodNet Queensland for their support in providing data, advice on analysis, and feedback on draft report. I am grateful to my supervisors for identifying this as a suitable project and providing feedback on the final version of this Chapter. I also acknowledge public health units and pathology laboratories for providing cases' information and diagnosis results and for their public health activities for the management of the notified cases.

Abstract

Introduction: Shiga toxin-producing *Escherichia coli* (STEC) infection is a notifiable condition in Queensland. Diagnosis of STEC infections occurs following stool testing and identification by pathology laboratories. Since 2020, Queensland has been receiving notifications of STEC infection following diagnosis by an interstate pathology laboratory that provides diagnostic services for alternative health practitioners including naturopath and nutritionist. This study was aimed to understand the significance of the interstate laboratory notifications and assist with the review of guidelines for the surveillance and management of STEC cases.

Methods: This is a descriptive epidemiological study comparing STEC cases diagnosed by the alternative medicine diagnostic laboratory, specialty pathology laboratory (SPL) based in Victoria with those notified by other pathology laboratories. The study period included STEC cases notified from January 2020 to December 2022 and the analyses compared demographic characteristics, symptoms, and laboratory test results. Cases were followed up by public health units as a part of routine case management.

Result: In Queensland, the average annual rate of STEC notification over the study period was 0.61 (95% CI 0.50–0.75) per 100,000 population per year. Of the total 96 STEC cases, 68% (n=65) were notified by other pathology laboratories and 32% (n=31) by SPL. A majority of SPL cases (85%) were identified after consultation with non-medical practitioners. A higher proportion of the other pathology laboratories cases compared to SPL cases were symptomatic (88% vs 55%) ($P=0.001$), hospitalised (44% vs none) ($P<0.001$), experienced bloody diarrhoea (71% vs 6% of diarrhoeal cases) ($P<0.001$), and developed haemolytic uraemic syndrome (14% vs none). STEC O157 (21%), which can cause severe disease was detected only among other pathology laboratories cases. Cases possessing the *stx2* gene only were detected at a higher frequency among other pathology laboratories cases (51%) compared to SPL cases (35%).

Conclusion: Since 2020, Queensland Health has received a substantial number of asymptomatic and pauci-symptomatic STEC notifications from SPL. A change in testing practice has contributed to an increase of asymptomatic STEC case notifications in Queensland. Future guidelines for the management of such cases should be based on the assessment of clinical presentation and STEC pathogenicity determined by laboratory diagnosis.

1. Introduction

Shiga toxin-producing *Escherichia coli* (STEC) or Verotoxigenic *Escherichia coli* (VTEC) are causative agents of gastrointestinal disease associated with ingestion of contaminated food or water, contact with infected animals, and person to person transmission (1, 2). Infection can result in asymptomatic or symptomatic clinical presentations ranging from vomiting, abdominal pain, mild non-bloody diarrhoea to bloody diarrhoea, and haemolytic uraemic syndrome (HUS) (3). It is estimated that up to 10% of STEC cases develop HUS with a case fatality rate of 3–5% (4). The incubation period for STEC infection ranges from 3–8 days (average 3–4 days) (4). HUS develops after average duration of 5–13 days from diarrhoea onset (5). It is characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal failure (6). Approximately 40–60% of children with enteropathic HUS will require dialysis, and 3–5% die (6).

STEC can be detected by stool culture in 30–69% of HUS patients for a short period of time after onset (7). STEC has been isolated from asymptomatic carriers during investigations of outbreaks, intrafamilial infections, and from sporadic patients (8, 9). A study in Japan estimated the incidence of asymptomatic STEC infection among healthy adults to be 84.2/100,000 population per year (8). This compares with an annual notification rate of approximately 2.7–3.5/100,000 population in Japan (8). Likewise, a study in Belgium has demonstrated that approximately one-third of STEC infected individuals did not develop diarrhoea or HUS and 17.5% did not suffer from any gastrointestinal symptoms (10). These findings demonstrate that asymptomatic infections occur and are likely to remain undetected, making the incidence of STEC higher than reported through routine surveillance. The World Health Organization estimated that foodborne STEC caused 1 million illnesses in 2010, which resulted in >100 deaths and nearly 13,000 disability-adjusted life years (11, 12). The incidence rate ranged from 1.6 to 1.8 per 100,000 population per year in the European Union countries (2020) and the United States (2017), respectively (13, 14). In Australia, the rate of STEC notifications in 2022 was 3.2 per 100,000 population per year (15). The overall increase in STEC notification has been attributed to change in laboratory practices (routine testing using nucleic acid detection in addition to clinical requests) and availability of molecular diagnostic testing (16, 17).

Laboratory confirmed STEC is nationally notifiable in Australia (18). A case is confirmed based on laboratory definitive evidence, either isolation by culture or detection of *stx* gene/s by nucleic acid testing of faeces (18). Surveillance in Queensland has identified six community STEC outbreaks between 2001 and 2013 (two zoonotic transmission, two person to person, one contaminated water, one unknown) (18). A large STEC outbreak including 55 primary

infections and two secondary infections was reported in August 2013 related to contact with infected animals at the state agricultural show (18, 19). An STEC outbreak was also reported in a rural school camp associated with contaminated tank water (20).

In Queensland, STEC cases are notified by pathology laboratories after testing requested by clinicians. Since 2020, there have been cases notified to Queensland Health from specialty pathology laboratory (SPL), a private diagnostic laboratory in Melbourne, Victoria. Routine investigation of these cases ascertained that most cases had stool specimens referred to SPL from complementary health practitioners (naturopaths and nutritionists). The patients were either asymptomatic or presented with a range of non-specific symptoms like acne, eczema, bloating, and constipation. All notified cases of STEC infection are routinely investigated in Queensland to determine the likely source of infection and prevent further transmission. This descriptive epidemiological review was conducted in response to the emergence of asymptomatic and pauci-symptomatic cases of STEC in Queensland, and to understand the significance and contribution of SPL cases to this increase. This analysis was also used to inform a review of local guidelines for the surveillance and management of STEC cases.

2. Methods

2.1. Study design

The investigation involved a case-series study with the descriptive analysis of the confirmed STEC cases notified to Queensland Health from January 2020 to December 2022. After notification by pathology laboratories, cases were followed up by public health units (PHUs) as a part of routine surveillance response to identify and manage potential public health risks and identify outbreaks to enable a rapid public health response.

2.2. Case definition

The notified STEC cases were confirmed by laboratory definitive evidence. As per the national and Queensland Health guidelines, the laboratory definitive evidence refers to the following criteria (21, 22):

Isolation of STEC from faeces OR Identification of the gene/s associated with the production of Shiga toxin (*stx1* and/or *stx2*) or Vero toxin in *Escherichia coli* by nucleic acid testing on clinical isolate or fresh faeces.

An STEC case is notified as both STEC and HUS, when the case definition for HUS is met (18). Two or more linked cases involving more than one household meets the criteria of a community outbreak (18).

2.3. Study population

All cases notified to Queensland Health by both private and public laboratories during the study period (2020–2022) were included. Data were extracted from the Queensland Health Notifiable Conditions System (NoCS) and case report forms and analysed separately as notification from SPL and other pathology laboratories.

2.4. Study variables

Data obtained from NoCS included the following variables for comparative analysis: Date of birth, sex, PHU, notification date, clinical presentation (date of onset, symptomatic features, hospitalisation status), and laboratory diagnosis (date of specimen collection, culture, serotyping (O, H) results, and detection of STEC genes (*stx*, *eaeA*, *ehxA*)).

2.5. Laboratory testing

Diagnosis of STEC was performed by SPL using multiplex PCR for enteric pathogens on the faecal samples of patients. STEC confirmation and characterisation of culture-positive isolates was performed by the Microbiology Diagnostic Unit Public Health Laboratory (Doherty Institute, University of Melbourne).

Other STEC cases referred to in this study were tested by pathology laboratories and/or the Queensland STEC reference laboratory (Public Health Microbiology, Forensic and Scientific Services, Queensland Health) using PCR and/or culture. These tests were based on clinician or public health physician request or medical microbiologist approved referral for faeces with blood present or symptomatic patients where no other faecal pathogen had been identified. Further confirmatory testing (culture, PCR, serotyping, genomic analysis) were performed by the reference laboratory.

2.6. Stakeholder engagement

This epidemiological review was conducted by the Communicable Diseases Branch and OzFoodNet, Queensland Health. It involved engagement with the Queensland Health STEC Guidelines Working Group including representatives from PHUs, OzFoodNet, and Forensic and Scientific Services of Queensland for obtaining information on notifications, laboratory diagnosis, and dissemination of the findings from this study.

2.7. Data management and analysis

Cases were categorised into age groups based on age calculated from date of birth and the episode date (earliest available of the following dates: onset date, specimen collection date, and notification date). Missing or blank fields were categorised as unknown. Cases were categorised as symptomatic based on the presence of one or more of the symptoms of acute illness: diarrhoea, abdominal pain, and vomiting.

A descriptive analysis was performed reporting counts and percentage of the cases by notifying pathology laboratories (SPL or other pathology laboratories), year, age groups, sex, hospitalisation, notifying PHU, Hospital and Health Service (HHS), HUS clinical presentation, symptomatic features, and laboratory diagnosis based on culture, serotyping, and STEC genes (*stx1*, *stx2*, *eaeA*, *ehxA*). The number of cases were plotted on an epidemiological curve for each month of the year of episode date. Annual notification rates were calculated as the number of cases per 100,000 population per year using the Australian Bureau of Statistics (ABS) mid-year population of Queensland for 2020, 2021, and 2022 (23). Incidence rates by HHS were calculated based on ABS modified data derived by the Statistical Services Branch, Queensland Health (24). The Chi squared tests were performed to determine whether the distribution of STEC cases by demographic characteristics or clinical presentations differed between SPL and other pathology laboratories. Confidence intervals of proportions and *P*-values were calculated. Data were analysed and managed using Microsoft Excel Version 2202 (Microsoft, Redmond, Washington) and Stata version SE 16.1 (StataCorp, College Station, TX).

2.8. Ethics

The study was conducted as a part of surveillance of a notifiable disease under the Public Health Act 2005 and the Queensland Public Health Regulation 2018. Ethics approval was available from the Australian National University (protocol: 2017/909) under an existing approval for the investigation of an acute public health problem or outbreak by Master of Philosophy in Applied Epidemiology students.

3. Results

During 2020–2022, a total of 96 STEC cases were notified in Queensland, 31 (32%) from SPL and 65 (68%) from other pathology laboratories (Table 1, Figure 1). There were no STEC notifications from SPL prior to the study period. A higher overall notification rate in 2022 was contributed by SPL (Table 1).

Table 1. Notification rate of STEC cases by year and notifying pathology laboratories, Queensland, 2020–2022

Year	SPL		Other pathology laboratories		All cases	
	Cases	Rate* (95% CI)	Cases	Rate** (95% CI)	Total cases	Rate* (95% CI)
2020	9	0.17 (0.09–0.33)	21	0.41 (0.26–0.62)	30	0.58 (0.41–0.83)
2021	8	0.15 (0.08–0.31)	22	0.42 (0.28–0.64)	30	0.58 (0.40–0.82)
2022	14	0.26 (0.16–0.44)	22	0.41 (0.27–0.63)	36	0.68 (0.49–0.94)
All cases	31	0.20 (0.14–0.28)	65	0.41 (0.32–0.53)	96	0.61 (0.50–0.75)

*Rate calculated per 100,000 population per year, SPL: Specialty pathology laboratory

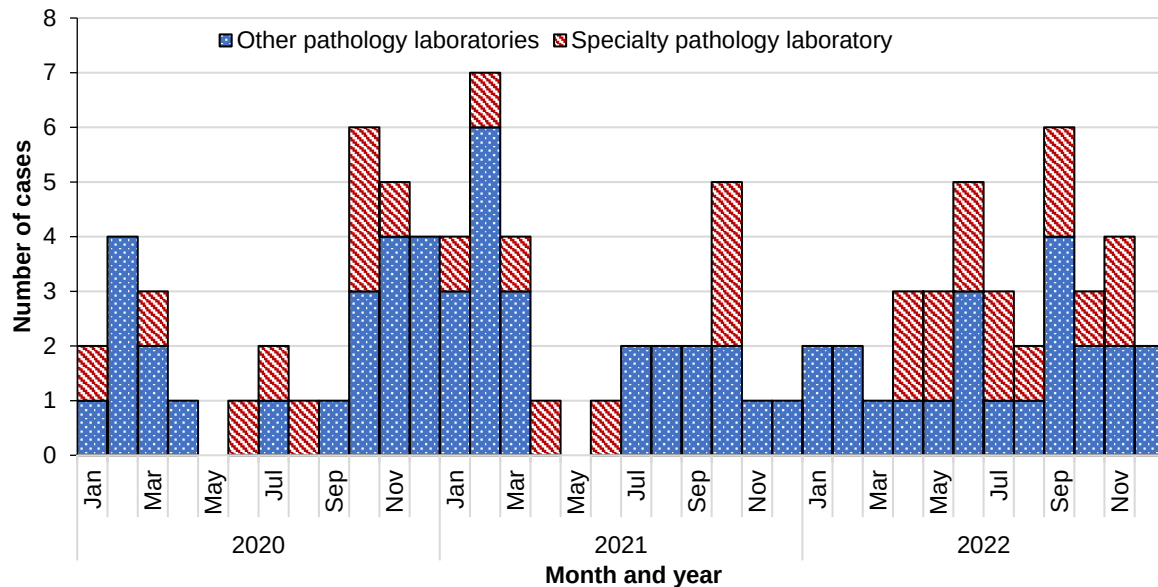


Figure 1. STEC cases by month and year of episode date and notifying laboratories, Queensland, 2020–2022

SPL notified cases were more commonly female (81%) compared to other pathology laboratories notified cases (43%) ($P=0.001$) (Table 2). The median age of the cases notified by the laboratories was similar, although the range differed by age and sex (Table 2, Figure 2). A higher proportion of other pathology laboratories cases were symptomatic (88% vs 55%, $P=0.001$) and hospitalised (44% vs none, $P<0.001$) compared the SPL cases (Table 2, Figure 3). Of the other pathology laboratories cases, 58% (37/64) experienced bloody diarrhoea compared to 3% (1/29) of SPL cases ($P<0.001$) (Table 2).

Table 2. Demographic characteristics STEC cases by pathology laboratories, Queensland, 2020–2022

Characteristics	SPL cases		Other pathology laboratories cases		P
	n (%)	95% CI (%)	n (%)	95% CI (%)	
Sex (n %)					
Male	6/31 (19%)	9–38	37/65 (57%)	44–69	0.001
Female	25/31 (81%)	62–91	28/65 (43%)	31–55	
Median age (range)#	35 (1–65)		31 (<1–90)		
Clinical presentation*					
Symptomatic**	16/29 (55%)	36–73	56/64 (88%)	77–94	0.001
Bloody diarrhoea**	1/29 (3%)	0–22	37/64 (58%)	45–69	<0.001
Bloody diarrhoea (% diarrhoea cases)	1/14 (7%)	1–42	37/52 (71%)	57–82	<0.001
HUS* (% of all cases)	0		9/64 (14%)	7–25	0.024
Hospitalised*	0		27/62 (44%)	32–56	<0.001
Household contacts***	0		6/65 (9%)	4–19	0.174

[#]Median age and range in years, ^{*}Excludes cases with unknown characteristics, ^{**}% of symptomatic cases with known symptomatic status (symptomatic and asymptomatic), ^{***} Includes contacts of a case and are cases of the study population; SPL: Specialty pathology laboratory

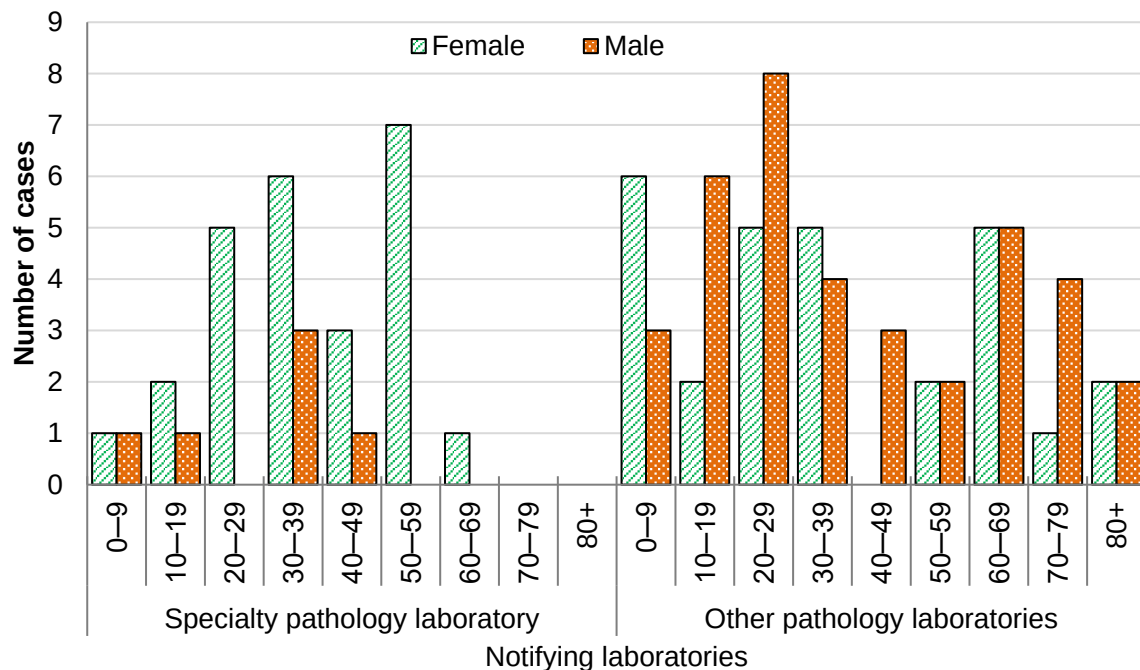
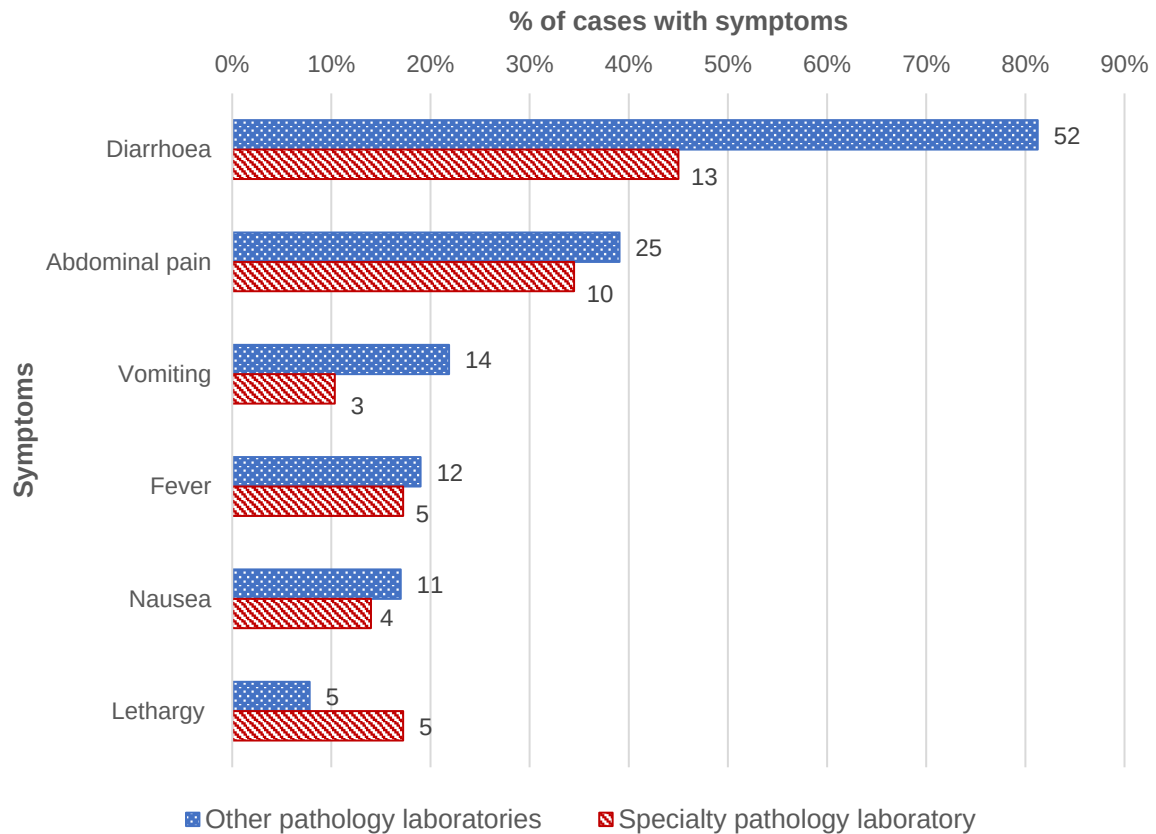


Figure 2. STEC cases by pathology laboratories, age group and sex, Queensland, 2020–2022



% of all the cases with known symptomatic status (symptomatic and asymptomatic) for each notifying laboratories; A case can have one or more symptoms

Figure 3. STEC cases by pathology laboratories and symptoms, Queensland 2020–2022

There were no reports of HUS among cases diagnosed by SPL; HUS was reported in 14% (9/64) of the cases notified by other pathology laboratories (Tables 2 and 3). HUS cases were children and older adults (age range: <1-85 years) including, 56% females (n=5) and 44% males (n=4) (Table 3).

Table 3. Other pathology laboratories diagnosed STEC cases with HUS, Queensland, 2020–2022

Age	Sex	Year	Hospitalised	Serotype	stx1	stx2	eaeA	ehxA
0–9	F	2020	Yes	NA	-	+	NA	NA
0–9	F	2021	Yes	O111 H8	+	+	+	+
0–9	F	2022	Yes	NA	-	+	NA	NA
0–9	M	2022	Yes	O2 H1	-	+	NA	NA
50–59	F	2022	Yes	O158 H42	-	+	-	+
50–59	M	2022	NA	O157	-	+	NA	NA
60–69	F	2020	Yes	NA	-	+	NA	NA
60–69	M	2020	Yes	NA	-	+	NA	NA
80+	M	2020	Yes	O82 H19	-	+	-	+

F: Female, M: Male, NA: Data not available, +: Positive, -: Negative

The highest proportion of all notified STEC cases were from Metro South HHS (21%) followed by Metro North (16%) and Gold Coast (16%) (Figure 4). However, the average annual rate of notification was highest for Central Queensland, Wide Bay, and Darling Downs (1.2 per 100,000 population per year) compared to Metro North and Metro South (0.5 per 100,000 population per year) and Gold Coast (0.8 per 100,000 population per year).

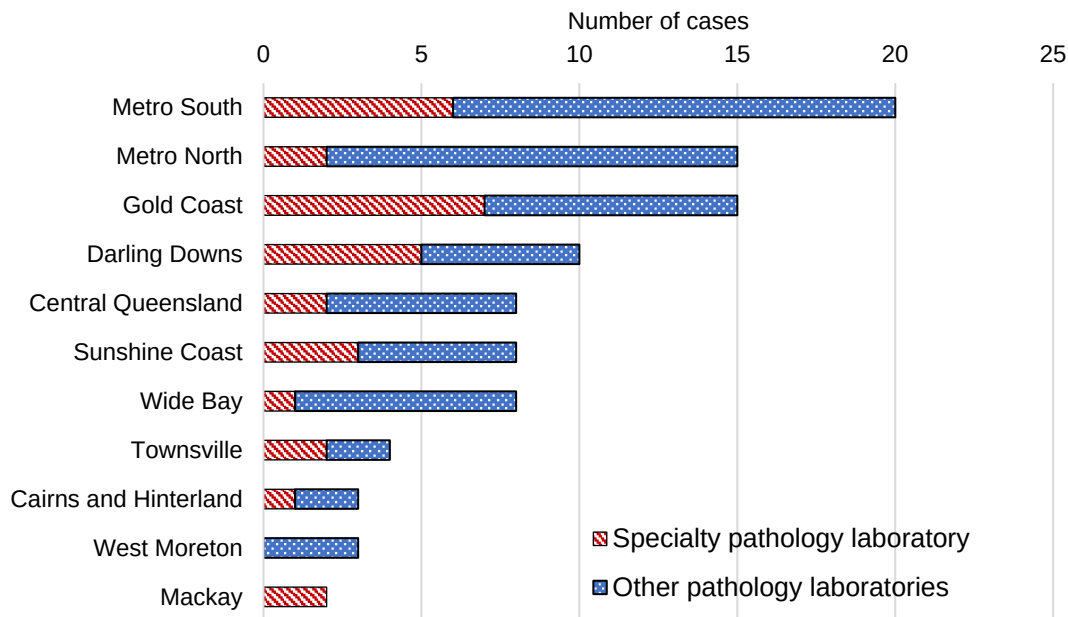


Figure 4. STEC cases notified by laboratories and Hospital and Health Services, Queensland, 2020–2022

Of the SPL notified cases, 85% (23/27) were identified after consultation with alternative health practitioners — naturopath (n=19) or nutritionist (n=4) and 15% (4/27) identified by medical practitioners (Figure 5). Whereas, of the other pathology laboratories cases, 92% (60/65) were known to have consulted medical practitioners, 6% (4/65) were identified during public health follow up as a close contact of a previously reported case, 2% (1/65) diagnosed after faecal donor screening, and none were identified after consultation with non-medical practitioners.

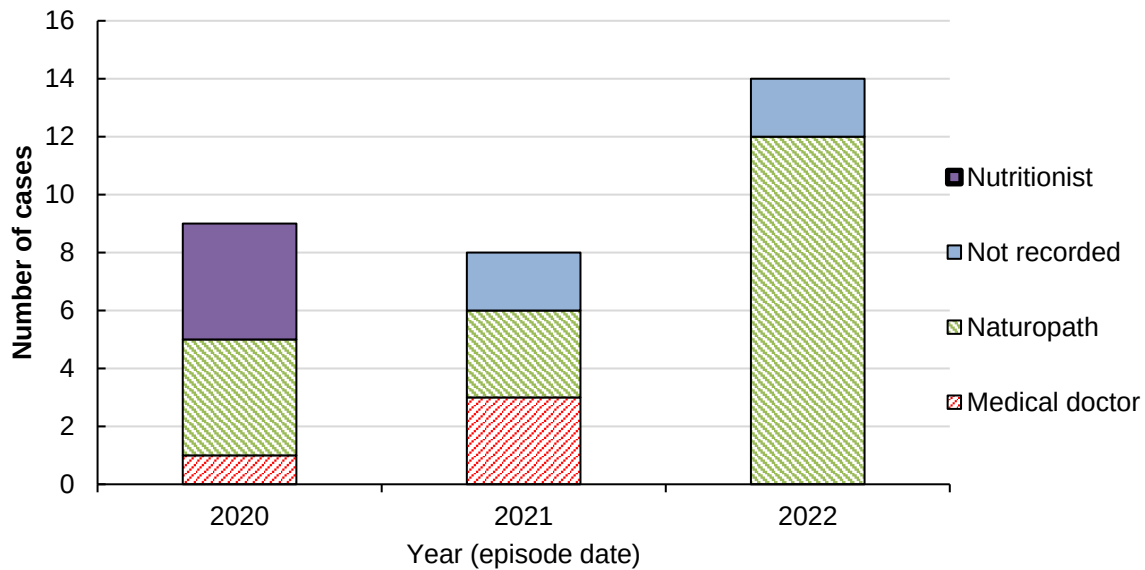


Figure 5. Specialty pathology laboratory notified STEC cases by year and first consultation, Queensland 2020–2022

Laboratory culture was positive for 67% of SPL cases compared to 42% of the other laboratory pathology laboratories notified cases (Table 4). Serotype was identified among 50% (48/96) of all the cases and the most common serotypes were O128:H2 (20%) and O91:H14 (20%) among SPL cases and O157:H- (11%) among other pathology laboratories cases (Table 4). *Stx1* only cases were comparable among both SPL and other pathology laboratories. Both *stx1* and *stx2* were detected in higher proportion by SPL laboratory, whereas *stx2* only and *eaeA* were detected in a higher proportion of the other pathology laboratories cases (Table 4).

Of the other pathology laboratories cases, 64% (21/33) with *stx2* gene only had bloody diarrhoea compared to 50% (7/14) with *stx1* only and 50% (9/18) with both *stx1* and *stx2* genes. Only one SPL case with bloody diarrhoea had *stx2* gene detected. Among other pathology laboratories cases, 89% (8/9) of HUS cases had *stx2* gene only detected and 24% (8/33) with *stx2* developed HUS (Tables 3 and 4). Of the other pathology laboratories cases with *stx2* gene only, 97% (32/33) were symptomatic and 63% (20/32) were hospitalised. Among SPL cases with *stx2* gene only, 63% (5/8) were symptomatic and none were hospitalised.

Table 4. Laboratory test results of notified STEC cases by notifying laboratories, Queensland, 2020–2022*

Test results	SPL cases	Other pathology laboratories cases
Laboratory culture		
Positive	20/30 (67%)	27/65 (42%)
Negative	10/30 (33%)	38/65 (58%)
Serotypes		
O3 H21	1/20 (5%)	–
O8 H8	1/20 (5%)	–
O2 H1	–	1/28 (4%)
O26 H11	–	2/28 (7%)
O28/O42 H25	–	1/28 (4%)
O30/O8 H25	1/20 (5%)	–
O39 H21	1/20 (5%)	–
O76 H7	1/20 (5%)	–
O82 H19	–	1/28 (4%)
O91 H14	4/20 (20%)	1/28 (4%)
O91 H21	–	1/28 (4%)
O104 H16	1/20 (5%)	–
O111 H8	1/20 (5%)	2/28 (7%)
O112 H2	1/20 (5%)	–
O112 H19	1/20 (5%)	–
O117 H7	–	2/28 (7%)
O128 H2	4/20 (20%)	2/28 (7%)
O128 H21	–	2/28 (7%)
O139 H8	–	1/28 (4%)
O145 H28	–	2/28 (7%)
O146 H28	1/20 (5%)	–
O157	–	2/28 (7%)
O157 H-	–	3/28 (11%)
O157 H7	–	1/28 (4%)
O158 H42	–	1/28 (4%)
ONT H7	–	1/28 (4%)
ONT H19	1/20 (5%)	–
ONT H21	1/20 (5%)	–
O- H2	–	1/28 (4%)
H7	–	1/28 (4%)
Stx genes		
Stx 1 positive; Stx 2 negative	6/26 (23%)	14/65 (22%)
Stx 2 positive; Stx 1 negative	9/26 (35%)	33/65 (51%)
Stx 1 positive; Stx 2 positive	11/26 (42%)	18/65 (28%)
eaeA (Intimin)		
Positive	1/5 (20%)	20/39 (51%)
Negative	4/5 (80%)	19/39 (49%)
ehxA (Enterohemolysin)		
Positive	4/4 (100%)	26/36 (72%)
Negative	–	10/36 (28%)

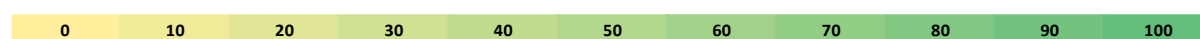
*Unknown excluded from denominators; –: No observation

Data on subtypes of *stx* were available for 18 cases (SPL=4, other pathology laboratories=14) (Table 5). Among the other pathology laboratories cases, a higher proportion of cases with only *stx2a* developed bloody diarrhoea, symptom, HUS and/or were hospitalised. *stx2b* was detected with *stx1a/stx1c* in all the *stx* subtyped SPL cases, where a majority developed symptoms, but none were hospitalised or reported bloody diarrhoea.

Table 5. Proportion of *stx* subtyped STEC cases with clinical presentation and hospitalisation status by notifying laboratories, Queensland, 2020–2022

Stx sub types	Other pathology laboratories (n=14)					SPL (n=4)				
	n	HUS	BD	SYM	HOS	n	HUS	BD	SYM	HOS
1a	1	0%	0%	100%	0%	0	NA	NA	NA	NA
2a	6	50%	67%	100%	83%	0	NA	NA	NA	NA
2b	1	0%	0%	100%	100%	0	NA	NA	NA	NA
1a & 2a	1	0%	0%	100%	0%	0	NA	NA	NA	NA
1a & 2b	1	0%	0%	0%	0%	3	0%	0%	67%	0%
1a & 2c	2	0%	50%	100%	50%	0	NA	NA	NA	NA
1c & 2b	2	0%	50%	50%	0%	1	0%	0%	100%	0%

Scale of percent of cases



*n: number of cases; HUS: Haemolytic uraemic syndrome; BD: Bloody diarrhoea; SYM: Symptomatic; HOS: Hospitalised; NA: Not applicable; SPL: Specialty pathology laboratory

4. Discussion

STEC cases have been increasing in Australia and they remain under-reported due to occurrence of asymptomatic infections (16, 25). In response to the emergence of asymptomatic or pauci-symptomatic STEC cases diagnosed by a single laboratory following consultant with alternative health practitioners — we undertook a rapid review of recent cases in Queensland. During the study period (2020–2022), 85% of the SPL cases were tested after their visit to non-medical practitioners and 38% were asymptomatic. The initial diagnostic test was performed using a multiplex-PCR platform for enteric pathogens by the laboratory as opposed to stool culture. Hence, these cases were identified through a new notification pathway and changes in laboratory testing practices and methods.

Studies have shown that STEC PCR assays have sensitivity and specificity of 96–100% (26, 27). *stx* genes can be detected in stool specimens even when the bacterial culture is negative (28). Higher sensitivity of PCR assays can thus have an impact on increase in notifications. Some SPL diagnosed cases presented with insignificant or non-gastrointestinal related symptoms. These cases may have remained unidentified due to asymptomatic or mild clinical presentations not causing acute illness. A higher proportion of cases were also notified among females by SPL. It is likely to be due to differences in health seeking behaviour such as consultation for non-medical reasons like diet and lifestyle.

A higher proportion of other pathology laboratories cases were symptomatic, reported bloody diarrhoea, were hospitalised, and developed HUS compared to SPL cases. HUS (n=9) was diagnosed only among other pathology laboratories cases. Studies have shown that infection with STEC expressing *stx2/stx2a* only is more likely to develop HUS compared to STEC with *stx1/stx1a* only or both *stx1a* and *stx2a* (29-32). Stx is an AB₅ toxin that inhibits protein synthesis of susceptible eukaryotic cells (29). *stx1a* B subunit reduces pathogenicity of *stx2a* by competing to bind with the target cells and thus protects from cytotoxicity of *stx2a* (29). In this study, *stx2* gene only detection was 16% higher among other pathology laboratories cases compared to SPL cases. Of the *stx* subtyped cases, *stx2a* gene was detected only among other pathology laboratories cases and a majority of these presented with a combination of bloody diarrhoea, symptoms, or HUS and were hospitalised.

Serogroup O91:H21 and serotype O157 known to cause severe disease (33, 34), were identified only among other pathology laboratories cases. Likewise, *eaeA* (Intimin) which is essential in intimate attachment of STEC to enterocytes (35), was detected in higher proportion of other pathology laboratories cases and others have shown that *eaeA* positive *E.coli* are correlated with diarrhoea in adults (36). A range of STEC virulence factors and host factors can thus influence clinical presentation and outcome of the disease (37, 38). Although causal inference of these factors with severity of disease could not be established, the laboratory reports correspond to epidemiological investigation and published literature (9, 29, 30, 37, 38), indicating less severe disease outcome among SPL cases.

One of the limitations of this investigation is data completeness on laboratory test results including serotype and detection of STEC genes. Epidemiological data from case interviews with genomic analysis can provide useful information to determine disease outcome, secondary transmission, and magnitude of cluster. Although there are limitations with the availability of complete laboratory test results, this investigation provides insight into the observation of increasing mild STEC infection and changes in laboratory testing practices that have contributed to an overall increasing in STEC notifications in Queensland.

In line with the Queensland Health guidelines for public health units, all notified STEC cases are investigated and followed up to identify source of infection (ingestion of suspected food, contact with animals, drinking contaminated water) (18). In Queensland, cases are excluded from working in high-risk settings (childcare attendance or worker, food handler, health care worker) during exposure and/or infectious period (18). All cases and household contacts are followed up until evidence of microbiological clearance (two successive negative stool samples 24 hours apart) (18). Asymptomatic STEC infection in household contacts can be a source of person-to-person transmission (39). Shedding of STEC can occur for a prolonged

period from asymptomatic carriers for 4 to >10 months (9, 40). Evidence and guidance for managing asymptomatic cases is varied and less clear (41). In low-risk settings, treatment and exclusion of asymptomatic cases may not be necessary (41). The current guidelines require exclusion of asymptomatic contacts from attending childcare and workplace (18). Hence, management of STEC cases requires resources for follow up and testing of both symptomatic and asymptomatic cases. It differs with other jurisdiction such as South Australia where not all cases are followed up and only those associated with high-risk groups, clusters or outbreaks are investigated (42). Likewise in the United Kingdom, STEC cases and contacts (symptomatic or asymptomatic) are managed based on risk group, diagnostic laboratory results and clinical history of patients (43). Therefore, notification of asymptomatic cases and changes in testing practices, as shown by this study, suggest a need to revise guidelines for the management of STEC cases in Queensland. Based on findings from this study, it is recommended that when cases are diagnosed by alternative health practitioners, they are not required to be followed up if they are asymptomatic, culture negative in laboratory diagnosis, and they do not work in high-risk settings.

5. Conclusion

This study highlighted an increase in STEC notifications in Queensland due to a new notification pathway and changes in laboratory testing practices and methods. There were differences in the disease outcomes observed between cases diagnosed by pathology laboratories referred by alternative health practitioners and medical practitioners. As Queensland's current STEC guidelines require follow up of all notified cases and contacts identified, there is a need for further consideration and revision of the guidelines. STEC cases may be better managed based on their clinical presentation, laboratory testing results, and identification of high-risk groups.

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Chapter III:

Investigation of an acute public health problem or threat

Part B

Using genomic surveillance for the investigation of COVID-19 clusters of a distinct sub-lineage of SARS-CoV-2, Queensland, 2023

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Prologue

A cluster of 15 COVID-19 cases related to a distinct sub-lineage of the Omicron strain was notified by the Forensic and Scientific Services (FSS), Queensland Health to the Communicable Diseases Branch on 20 March 2023. The cluster was identified as a part of monitoring of whole genome sequences of SARS-CoV-2 with 15 or more mutations compared to the closest known parental clade (referred as “long branch”). The cluster belonged to the sub-lineage CH.1.1 (from the parent lineage BA.2.75). This was later assigned sub-lineage FK.1, circulating in numerous countries but not considered variant of concern.

As of 19 April 2023, an additional 31 cases of this sub-lineage had been identified in Queensland. Approvals were obtained from Metro South, Metro North, West Moreton, Gold Coast, and Townsville Public Health Units (PHUs) to conduct an epidemiological investigation of cases from this cluster in the corresponding Hospital and Health Services. This Chapter describes the investigation that was conducted from 24 April 2023 to 19 May 2023.

My role

I was based at the Metro South PHU during the period to conduct case interviews. The aim of this investigation was to determine the source of infection of the cases and identify any additional cases who were household/family contacts. My role was to lead the investigation into this cluster. I was involved in designing a questionnaire for collecting information and contacting cases via telephone. I obtained additional information on laboratory testing and hospital records from databases. I identified the source of infection for cases, linked cases in sub-clusters, undertook the data analysis, and drafted a final report.

Lessons learned

This project was a great opportunity to develop my understanding of genomic surveillance. I could also apply my epidemiological skills to collate and analyse evidence collected through various sources. I learned to overcome challenges of communicating with cases and their family members. Lessons learned were the importance of clear communication; using lay terms in describing the situation to cases with empathy; and quickly obtaining information in a short time. This study was also useful to understand limitations of such investigation including selection bias in analysing data from only interviewed cases; recall issues in collecting information from notified cases; and obtaining limited information from household members on behalf of cases. I learned the importance of correctly interpreting genomic results and drawing conclusions based on both epidemiological evidence and laboratory test results.

Public health impact

This Chapter highlighted the importance of whole genome sequencing in understanding transmission dynamics of an infectious disease. The investigation identified the occurrence of hospital acquired infections of COVID-19. As there was ongoing transmission of SARS-CoV-2 in the community, there was also an increased risk of transmission in high-risk settings such as hospitals where patients are vulnerable to severe health outcomes due to other co-morbidities and age factors. Hospital acquired infections can not only prolong hospital stay but also result in more complex treatment and cause fatality of patients. Hence, infection prevention and control measures need to be taken promptly in high-risk settings to prevent further transmission of infectious diseases between patients, staff, and visitors.

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Abstract

Background: Genomic surveillance is useful to identify clusters and understand transmission pathways and the severity of COVID-19. An epidemiological investigation was conducted to determine the source of infection and identify possible links between clustering cases of SARS-CoV-2 Omicron BA.2.75, sub-variant FK.1.

Methods: Clustering cases of SARS-CoV-2 Omicron BA.2.75, sub-variant FK.1 (primary cases) from February 2023 to March 2023 were identified by the Forensic and Scientific Services (FSS), Queensland Health and notified to the Communicable Diseases Branch (CDB). The epidemiological investigation involved case interviews to determine the source of infection and identify cases who were household/family contacts. Additional data on primary cases were obtained from Queensland Health databases, including the Notifiable Conditions System (NoCS), the public hospital patient database (Viewer), and the public pathology laboratories database (AUSLAB). Cases were categorised as overseas acquired, hospital acquired, or community acquired, based on identified source of infection. Sub-clusters, including linked cases based on epidemiological evidence and genomic analysis were also identified.

Results: Of the 46 primary cases, 65% (n=30) acquired their infection while in hospital, 33% (n=15) in the community, and 2% (n=1) overseas. Median age of the cases was 78 years with a range of <1 year old to 93 years old. Two sub-clusters were from hospital A, with six and nine cases linked to each. The third sub-cluster was from hospital B with six linked cases. Of the 23 interviewed cases, 51 contacts (household/family members) were identified and of these, seven reported to have tested positive to COVID-19 during the investigation period. There were eight cases (27%, 8/30) who acquired infection in hospitals and later passed away within 6 to 26 days post their specimen collection date.

Conclusion: In this study, we report occurrence of an unrecognised hospital acquired infection of SARS-CoV-2 Omicron BA.2.75, sub-variant FK.1. Patients admitted to hospitals are vulnerable due to their age and other co-morbidities. In high-risk settings, monitoring for hospital acquired infection and implementing prevention and control guidelines promptly is still required to reduce further transmission and burden of COVID-19 within the vulnerable population of Queensland.

1. Background

The COVID-19 pandemic has highlighted the importance of timely whole genome sequencing (WGS) in the identification of pathogens, vaccine development, and disease surveillance (1, 2). WGS has been useful to identify the source of infection, understand transmission pathways and dynamics, and inform outbreak control measures (3). Since its emergence, SARS-CoV-2 has undergone substantial mutations, leading to the emergence of multiple variants, including those identified by the World Health Organization (WHO) as variants of concern (VOC), variants of interest (VOI), and variants under monitoring (VUMs) (4). Identifying variants of SARS-CoV-2 is useful in determining important virus-specific variations in clinical and public health metrics, including in basic reproduction number, incubation and infectious period, clinical presentation, severity, re-infection risk, attack rates, vaccine effectiveness, and developing therapeutics and diagnostics (5-7). The lineages of Omicron (B.1.1.529) are currently the most commonly circulating variants in the community (4, 8).

A cluster of 15 COVID-19 cases, which were related to a distinct sub-lineage of the Omicron strain, was notified by the Forensic and Scientific Services (FSS), Queensland Health to the Communicable Diseases Branch (CDB) on 20 March 2023. The cluster was identified as a part of routine monitoring of sequencing results of COVID-19 in Queensland by the FSS. The sequences were reported as part of a “long branch report” with 15 or more mutations, when compared to the closest known parental clade. These belonged to the sub-lineage CH.1.1 of a parent lineage BA.2.75 and were a part of a clade (CH.1.1 + S:D215G, S:Q613H, M_S212G). This has since been re-classified by the web application Pangolin as sub-lineage FK.1 (9). As of 8 March 2023, prevalence of this sub-lineage was 0.1% in Australia, an estimate based on available sequence data on CoV-Spectrum, an openly available genomic database (10).

The follow up investigation of COVID-19 cluster identification has become more challenging as we learn to live with COVID-19, especially as not all symptomatic people are tested, and of those that test positive only limited information is now routinely collected. However, monitoring WGS results can be useful to identify clusters and trace other cases based on their location, dates of onset, and specimen collection. This investigation was conducted to identify cases in a notified cluster and understand epidemiology and transmissibility dynamics of a distinct sub-lineage of SARS-CoV-2.

2. Methods

2.1. Study design

This cluster investigation involved a descriptive study design based on epidemiological evidence and WGS results. A list of clustering cases (primary cases) was generated on 19 April 2023. As a contact tracing officer, I interviewed cases, their household/family members or carers using a questionnaire (Appendix) to confirm their demographic details, understand potential source of infection, and identify contacts. They were followed up from 24 April 2023 to 20 May 2023. Geolocation of the primary cases, based on residential address, was used to identify premises type (residential, aged care, retirement community), and confirm possible links between cases and contacts in the cluster. Linkage of the cases at the same location was further investigated based on the onset date of the case or specimen collection date of the positive sample. Sub-clusters, including linked cases based on epidemiological evidence and genomic analysis were identified. PCR test positivity rate in Queensland and for the testing facilities, where sub-clusters were linked were also determined from January 2023 to April 2023.

2.2. Case definition

Notified primary cases were initially confirmed/diagnosed based on laboratory definitive evidence (detection of SARS-CoV-2 by nucleic acid testing/polymerase chain reaction (PCR)) (11). The cluster was later identified using WGS of SARS-CoV-2 and bioinformatic analysis. Primary cases were further classified as sequences with 15 or more mutations compared to the closest known parental clade using a “long branch” bioinformatic analysis developed at the FSS. This cluster belonged to the sub-lineage CH.1.1 (from the parent lineage BA.2.75) and was named FK.1.

Close contacts of primary cases in this investigation were defined as household/family contacts or contacts in a setting where a transmission event was known to have occurred. A close contact was considered to be a secondary case linked to the cluster based on laboratory definitive (positive PCR tests) or laboratory suggestive evidence (positive rapid antigen test) after 0–3 days of notification of the linked primary case.

Primary cases were categorised by source of infection as overseas acquired, hospital acquired, or community acquired based on the following epidemiological criteria (Table 1).

Table 1. Criteria for categorising primary cases based on source of infection from the epidemiological investigation

Source	Criteria
Overseas	Travelled overseas in the last 3 days* prior to specimen collection with no known local exposure
Community	- Admitted to a hospital due to COVID-19 as a principal diagnosis OR - Exposure period was in the community with no other known sources OR - Interviewed case informed to have acquired infection in community OR - Tested positive on the day of hospital admission or at the hospital emergency department
Hospital	- Exposure/incubation period covered hospital admission and discharge dates (0-8 days) (Evidence: Admission and discharge dates, initial tests negative followed by positive test in a hospital) OR - Interviewed cases identified themselves as close contacts in a hospital OR - Hospitalised close contact reported in laboratory test request notes OR - Admitted due to other reasons without COVID-19 symptoms and negative test on admission but tested positive in a hospital OR - Known primary cases in the same ward during incubation period (0–8 days) (Evidence: Hospital and laboratory test records)

** Average incubation period was considered 3 days (range 0–8 days) for the Omicron sub-lineages (11). If a case travelled overseas, but met the criteria of community or hospital acquired, the case was categorised under community or hospital acquired, respectively. If a community case met the criteria of hospital acquired, the case was categorised under hospital acquired infection*

Primary and secondary cases were linked in the following ways: Definitive link between primary cases and secondary cases occurred if a difference of specimen collection dates between the primary case and secondary cases was ≤ 28 days and they were at the same geolocation or were confirmed to be household/family contacts. Primary cases were linked to the sub-cluster based on both epidemiological evidence and genomic analysis. Epidemiological evidence included same source of infection, geolocation, and overlapping exposure/incubation period between cases. Genomic evidence referred to sequences that shared the same number of single nucleotide polymorphisms (SNPs) between the primary cases, i.e., that there were 0 SNPs between the clustering sequences.

2.3. Source of data

Demographic data and laboratory test results for primary cases were obtained from the Queensland Health Notifiable Conditions System (NoCS). Data included notification ID, name,

date of birth, vaccination status (doses and date received), hospital admission and discharge dates, sex, postcode, Aboriginal and/or Torres Strait Islander status (hereafter respectfully referred as First Nations), geolocation (latitude and longitude), confirmation status, Hospital and Health Service (HHS), Public Health Unit (PHU), premises type (based on address), facility (where the specimen was collected), specimen collection date, and notification date. Data on COVID-19 PCR tests performed in Queensland and by testing facilities were also retrieved from NoCS.

Genomic analysis results were provided by the FSS, Queensland Health. Additional information on travel history (2 weeks before specimen collection date), antivirals, hospitalisation, known source of infection, and close contacts were collected through case interviews. The Viewer, a web-based application including patient information from Queensland clinical public hospitals, administrative and speciality systems, and National My Health Record, were used to collect hospital admission details (hospital admission dates, discharge dates, admission reasons, and deaths). Data on sample collection wards and testing facilities were retrieved from AUSLAB (a database of public laboratory testing in Queensland).

2.4. Data analysis

Case data were summarised as counts and proportions by demographic characteristics, antivirals received, travel history, COVID-19 vaccination history, and source of infection. Median age of the primary cases was calculated. PCR test positivity rate was estimated as a total number of PCR positive tests divided by a total number of PCR tests (positive and negative) on the same sample collection date. Primary cases were matched with COVID-19 cases notified since 01 January 2022 based on the same geolocation (latitude and longitude) and address (unit, street number, suburb, and postcode). Data analysis, matching, and management were performed using Stata 16.1 (StataCorp, College Station, TX) and Microsoft Excel Version 2202 (Microsoft, Redmond, Washington). Cases were mapped using Microsoft Power BI Version 2.118.621.0 (Microsoft, Redmond, Washington) for visualisation purpose to identify possibly linked cases.

2.5. Phylogenetic analysis

The phylogenetic analysis for clustering cases was performed by the FSS. Sequences of primary cases were aligned to the reference sequence (coronavirus 2 isolate Wuhan-Hu-1 complete genome MN908947.3) by BWA-MEM2 (a sequence mapping tool) (12). A Phylogenetic Maximum Likelihood Tree was constructed using Queensland SARS-CoV-2

sequences (available at the time of reporting of the primary cases) which were aligned, and the phylogeny was generated based on a multiple sequence alignment between the sequences. The Maximum Likelihood Tree was generated by IQ-TREE2 (13). Tree visualization and plots were produced by ggplot2 and ggtree v3.1.0 (14) on R Studio v4.1.

2.6. Ethics

This cluster investigation was conducted under the auspices of the Queensland Public Health Act 2005 and Public Health regulation 2018. As a student participating in this response, my participation was also covered by a previously obtained the Australian National University ethics approval (protocol: 2017/909) for the investigation of an acute public health problem or outbreak.

3. Results

There were 46 notified primary cases identified in the cluster. Earliest specimen collection date was 1 February 2023 and latest was 30 March 2023 (Figure 1). All the cases were confirmed by PCR tests and the samples sequenced. Cases were from residential homes (85%), retirement community (9%), and aged care facilities (6%) at different locations (Figure 1). Of the total cases, for 50% (23/46) we were able to collect further information by interview, and of these, information was obtained from cases directly (52%, 12/23). For the remainder, information was collected from a household/family member or carer.

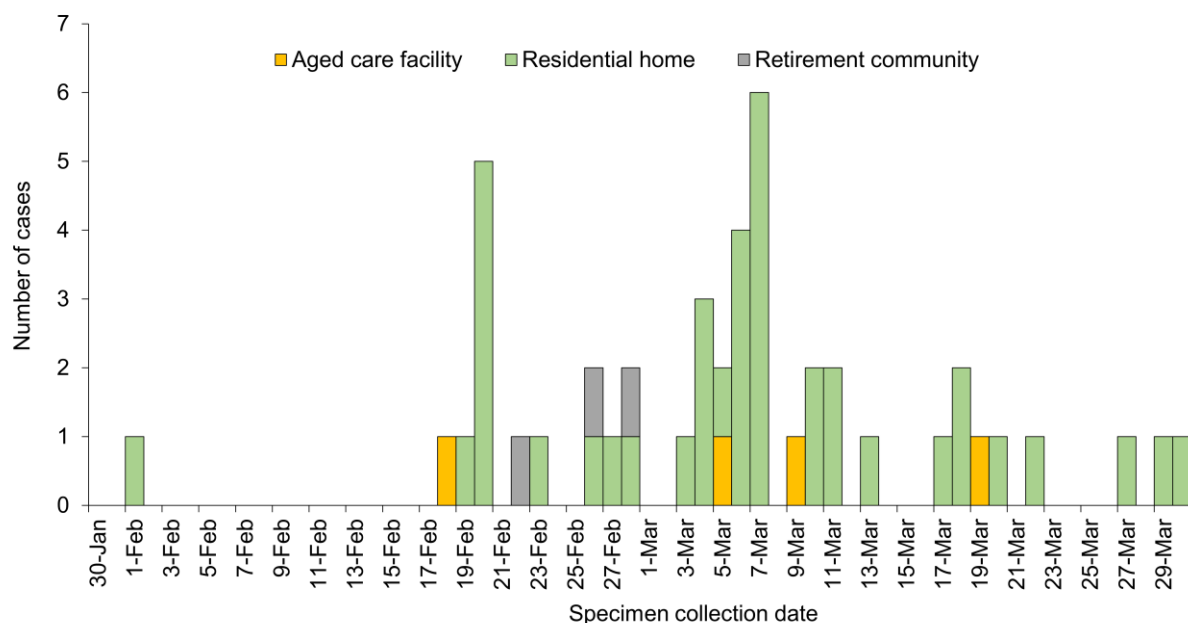


Figure 1. Cluster of COVID-19 cases of SARS-CoV-2 Omicron BA.2.75, sub-variant FK.1, by specimen collection date and premises type, Queensland, February 2023–March 2023

The cluster included 25 males (54%) and 21 females (46%) (Table 2). Age of the cases ranged from <1 year old to 93 years old (median age: 78 years). A majority of the cases were hospital patients at the time they tested positive for COVID-19 (n=44, 96%) and from Metro South HHS (n=39, 85%) (Table 2). Based on the source of infection identified, 65% (n=30) of the cases acquired infection in hospitals, 33% (n=15) in community, and 2% (n=1) overseas (Table 2, Figure 2). Of the 30 cases who acquired infection in hospital, 8 (27%) later passed away during the investigation period (median age at death 81 years, range 69–88 years). COVID-19 was recorded as a contributing factor of death for two of these cases and not recorded for the others.

Hospitalised cases met more than one criteria for their source of infection being hospital acquired. Common responses of the 13 interviewed cases who acquired infection in hospital settings were: *There were other COVID-19 cases in the same ward of the hospital before they tested positive (n=5); was in the hospital due to other reasons without prior COVID-19 symptoms (n=12); tested negative a few times during hospital stay before testing positive for COVID-19 (n=3); there was an outbreak in the hospital (n=2).*

Table 2. Characteristics of COVID-19 cluster cases by source of infection, Queensland, February–March 2023

Characteristics	Source of infection n (%)			Total n (%)
	Community	Hospital	Overseas	
Cases	15 (33%)	30 (65%)	1 (2%)	46
Sex				
Female	8 (53%)	13 (43%)	0	21 (46%)
Male	7 (47%)	17 (57%)	1 (100%)	25 (54%)
First Nations status	0	1/28 (4%)	0	1/46 (2%)
Age				
0–9	0	0	1 (100%)	1 (2%)
10–19	0	0	0	0
20–29	1 (7%)	0	0	0
30–39	0	1 (3%)	0	1 (2%)
40–49	1 (7%)	2 (7%)	0	3 (7%)
50–59	2 (13%)	1 (3%)	0	3 (7%)
60–69	4 (27%)	2 (7%)	0	6 (13%)
70–79	2 (7%)	10 (33%)	0	11 (24%)
80+	6 (40%)	14 (47%)	0	20 (44%)
Median age (years)	69 (29–91)	79 (37–93)	<1	78 (0–93)
Hospital and Health Service				
Gold Coast	2 (13%)	0	0	2 (4%)
Metro North	2 (13%)	0	0	2 (4%)
Metro South	9 (60%)	30 (100%)	0	39 (85%)
Townsville	1 (7%)	0	0	1 (2%)
West Moreton	1 (7%)	0	1 (100%)	2 (4%)
Died	0	8 (27%)	0	8 (17%)
Vaccination				
Unvaccinated	0	2 (7%)	1 (100%)	3 (7%)
One dose	2 (13%)	0	0	2 (4%)
Two doses	3 (20%)	1 (3%)	0	4 (9%)
Three doses	3 (20%)	10 (33%)	0	13 (28%)
Four doses	6 (40%)	16 (53%)	0	22 (48%)
Five doses	1 (7%)	1 (3%)	0	2 (4%)
Overseas travel	0	0	1/1 (100%)	1/23* (4%)
Hospitalised	13/15 (87%)	30/30 (100%)	1/1 (100%)	44/46 (96%)
Antivirals received	3/3 (100%)	6/10 (43%)	0	9/13* (69%)
Primary residential type				
Residential	13 (87%)	25 (83%)	1 (100%)	39 (85%)
Aged care facility	1 (7%)	3 (10%)	0	4 (9%)
Retirement community	1 (6%)	2 (7%)	0	3 (6%)

* Of the interviewed cases with only known characteristics

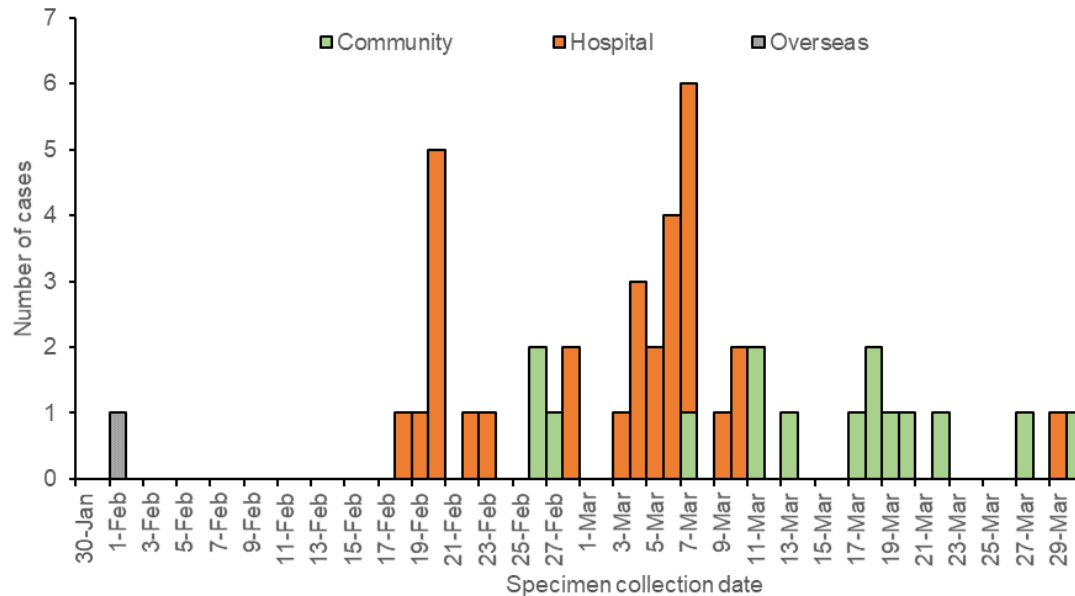


Figure 2. Notified cluster cases by source of infection, Queensland, February 2023–March 2023

The overseas acquired case was a child, <1 year old and had arrived from New Zealand, a day before testing COVID-19 positive. The case was symptomatic and tested at a hospital testing facility. Three close contacts of this case did not get tested and were not symptomatic. For the community acquired cases (n=15), epidemiological links to other primary cases were not able to be identified during this retrospective investigation, with two of these community acquired cases acquiring their infections from household members.

All the cases with hospital acquired infection were either from hospital A (n=20, 67%), hospital B (n=9, 30%), or hospital C (n=1, 3%). Based on the epidemiological investigation (evidence of sharing same ward/s with cases during hospital stay or same hospital) and the supporting genomic analysis, there were three sub-clusters identified related to hospital acquired infection (Figures 3 and 4, Appendix Figure 1). Two sub-clusters were from hospital A, with six and nine cases linked to each. The third sub-cluster was from hospital B with six linked cases.

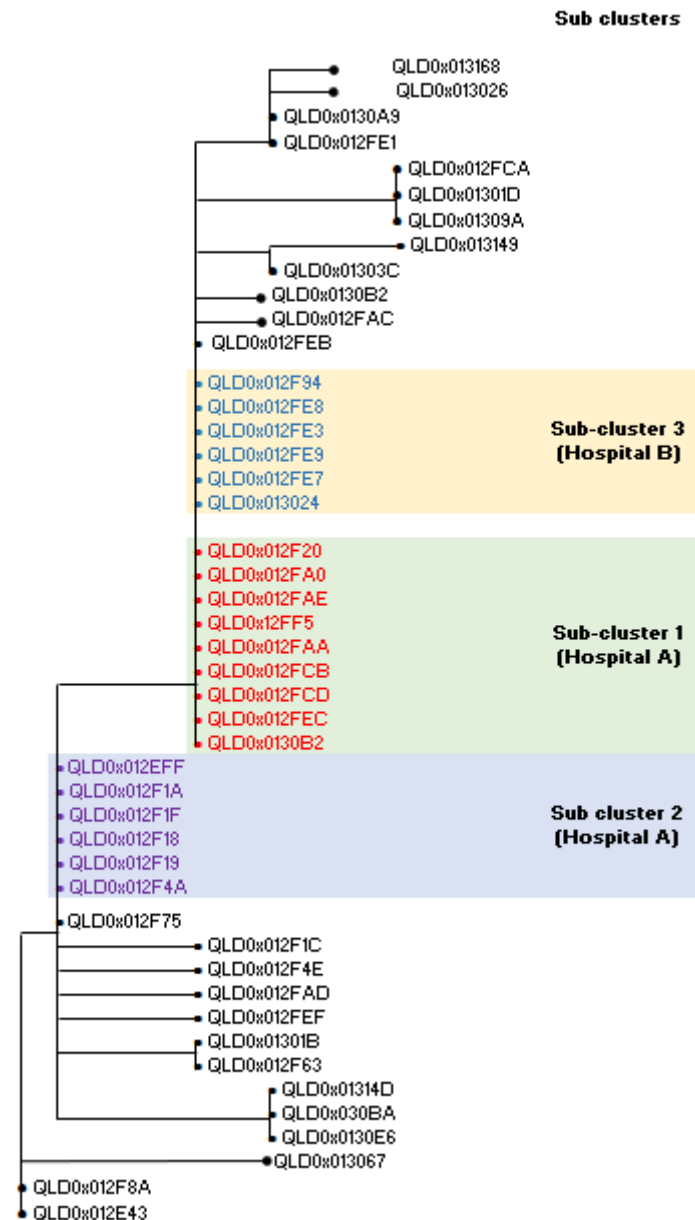


Figure 3. Phylogenetic tree of FK.1 sub-lineage cluster cases with the identified sub-clusters, Queensland, February 2023–March 2023

Five cases at hospital A and three cases at hospital B were not able to be linked to these sub-clusters, due to insufficient epidemiological evidence. One case acquired infection from hospital C, where a COVID-19 outbreak was reported by a household member (identified as a secondary case). This primary case who acquired infection at hospital C tested positive on admission at hospital A and no links with other cases were identified.

A total of 51 close contacts (household/family members) were identified from 23 cases interviewed. Of these close contacts, seven tested positive to COVID-19 (secondary cases), including one close contact of a primary case at hospital A, two close contacts related to hospital B, one close contact related to hospital C, and three contacts of a case in the

community (Figure 4). Six of the seven secondary cases were identified based on case interviews, geo-location, and positive test result after 0–3 days of the initial case notifications, while one was identified through a case interview.

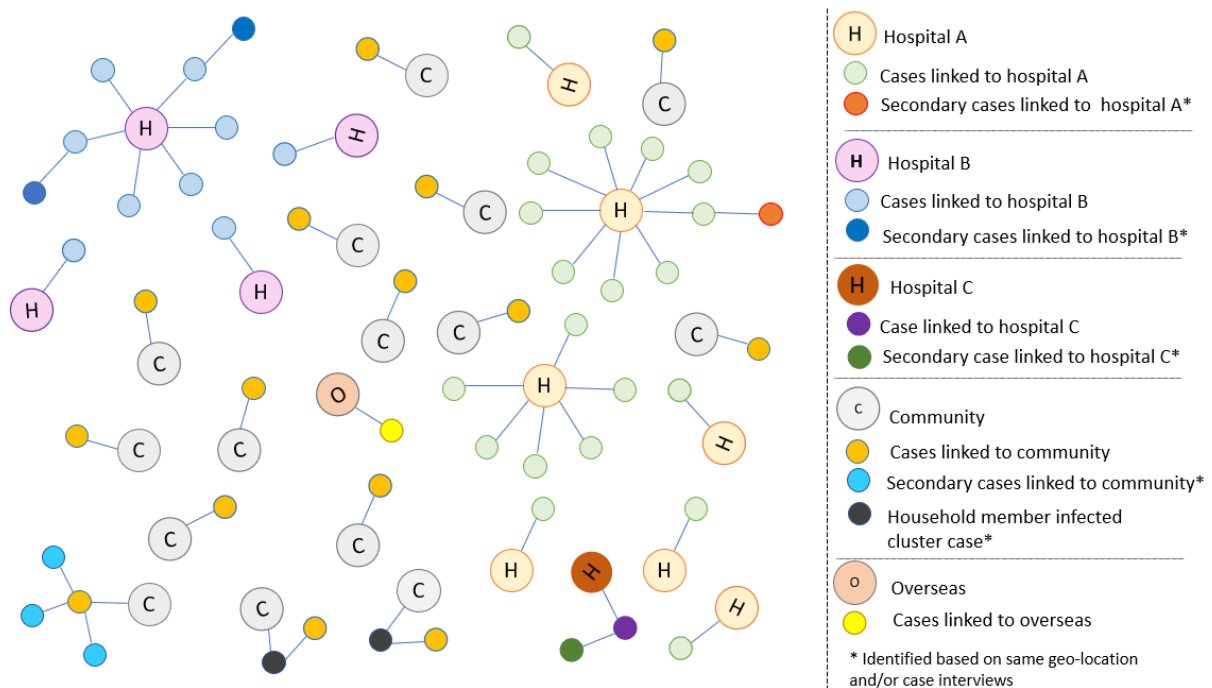


Figure 4. Transmission pathways with source of infection of COVID-19 cluster cases, February–March 2023

COVID-19 PCR test positivity rate was highest on the third week of January 2023 at hospital A (26%) and at hospital B (18%), which declined before increasing during identification of primary cases (Figure 5). Test positivity rate was 21% at hospital A on the eighth week and 16% at hospital B on the tenth week. In Queensland, the overall PCR test positivity rate was also highest (19%) in the first week of January 2023 but progressively declined in the subsequent weeks.

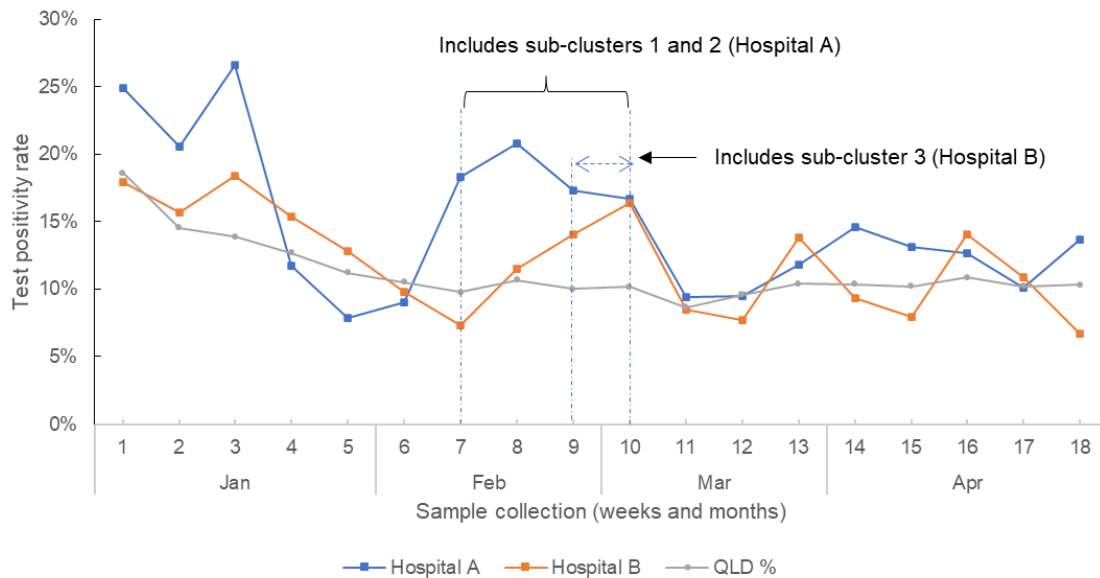


Figure 5. PCR test positivity rate by specimen collection (weeks) at Hospital A and B compared to Queensland (QLD), January 2023–April 2023

4. Discussion

During the global pandemic, WGS of SARS-CoV-2 and bioinformatic analysis played an important role, which enabled the identification of transmission pathways and early identification of new and emerging virus strains. With this investigation, we used genomic surveillance data and epidemiological data to identify cases in a cluster infected with newly identified sub-lineage FK.1. Current surveillance of COVID-19 does not require follow up of all cases, nor sequencing of all PCR positive cases. In Queensland, about 4–5% of PCR positive cases were sequenced in January 2023 (personal communication with Craig Thompson, Genomic Epidemiologist, FSS). To better understand this cluster, we were required to use different approaches including conducting case interviews and obtaining information from pathology laboratories and hospital records. The epidemiological investigation provided complementary evidence to the genomic analysis to understand source and transmission pathways between the notified cluster cases.

Identifying premises types (residential home, residential aged care facilities, retirement community) of the cluster cases was useful to understand distribution of cases in different settings. On investigation, none of these cases shared common premises type or geolocation based on residential address to indicate transmission at these specific sites. The addresses of notified cases were based on the laboratory test requests at the time of specimen collection. Therefore, residential type may not necessarily reflect the residence of the cases or location at the time of exposure. Case addresses were confirmed only for the interviewed cases. A majority of the cases (96%) were hospitalised patients, which may be due to sampling strategy

for WGS in Queensland at the time, which was prioritised for hospitalised cases, aged care facility residents, First Nations people, and individuals vaccinated against COVID-19 (15). Information on reason for admission whether due to COVID-19 or other health condition was unavailable at the time of notification.

Case interviews provided an important insight to understand possible sources of infection, hospitalisation reasons, and to identify potential secondary cases from household contacts. These data, coupled with laboratory testing and hospital data, showed that of the 46 cases identified in hospital testing facilities, 33% were likely to have acquired their infection in the community with no links identified between them. An overseas acquired case was identified in this genomic cluster and was a recently returned resident from New Zealand, where prevalence of 5.43% of this sub-lineage has been reported since December 2022, compared to Australia with a prevalence of 1.53% (10).

Based on epidemiological evidence, including known cases in same wards or hospital during hospital stay, no known COVID-19 symptoms and/or negative COVID-19 tests of the cases prior to hospital admission, 65% (n=30) of cases appear to have acquired infection at hospitals. This evidence, together with genomic results (based on same number of SNPs between cases), identified two sub-clusters at hospital A and one at hospital B. Although there were other cases with no SNP differences, due to inadequate epidemiological evidence, they were not able to be sub-clustered together. However, possible links between these cases cannot be ruled out. In 2020, a study in the United Kingdom reported that 17.6% of COVID-19 infections were hospital acquired infections (16). Hospital related transmission of SARS-CoV-2 was estimated in 42% of patients in China (17). Genomic analysis for the identification of clusters associated with hospital acquired infection have been well documented in other Australian jurisdictions (18-20).

We found that all the cases who acquired infection in the community or overseas were alive at the time of follow up. Crude fatality rate of 27% (8/30) for hospital acquired cases was high due to age factors and other comorbidities. A study on outbreaks in a residential aged care facility between December 2021 and February 2022 in the Gold Coast PHU, previously reported hospitalisation rate of 10.6% and case fatality rate of 6.5% for resident cases (21). In our study, seven household contacts of the 23 interviewed cases were identified as secondary cases (one of them linked to sub-cluster 1 at hospital A, two with sub-cluster 3 at hospital B, and one with hospital C). Therefore, secondary transmission from hospital to household/family members in the community were observed.

The highest positivity rate (18–26%) at hospitals A and B was in early January and positivity rate (16–21%) was still high during the period of cluster cases (February–March 2023). Overall

test positivity rate in Queensland was lower than the rates observed at the hospitals. Higher test positivity rate at the hospitals could be contributed to admission of COVID-19 patients for treatment and from ongoing transmission between patients and/or staff. Hence, there is likely to be additional cases linked to the clusters of hospital acquired infection than identified by this investigation.

This cluster investigation was based on information collected from different sources, so there were limitations. As genomic analysis results were available only for selected cases from hospitals due to current sampling strategy for WGS of COVID-19 positive samples for hospitalised cases, there was a selection bias in inclusion of cluster cases. Hence, the investigation was likely to capture higher number of cases in hospital settings compared to the overall cases in the community. However, this investigation was focussed on a distinct sub-lineage and the cluster included representative cases of this lineage identified through WGS during the investigation period. At the time of this investigation, the number of samples included for sequencing was approximately 100 per week, with about 90% of them successfully sequenced (i.e., passing bioinformatic quality controls) and BA.2.75 accounted for 25% of the sequenced samples in Queensland from 1 February 2023–30 April 2023 (personal communication with Craig Thompson, Genomic Epidemiologist, FSS). Secondly, only 50% of the cases in the cluster were able to be interviewed after 1–2 months of notification. Hence, there may have been recall issues due to delay in conducting case interviews and collecting information from family/household members. These recall errors were reduced by confirming demographic details, specific dates of testing, and hospital admission and discharge dates from laboratory and hospital records where possible. Index cases of sub-clusters could not be identified due to limitations of case information prior to the first notified case of the cluster. Lastly, genomic analyses depend on various factors including quality of specimen, viral loads, and completeness of sequencing information (19, 22, 23). Nevertheless, WGS analysis may be able to infer probable source of infection when epidemiological links are not determined (24).

This investigation represented a small number of cases of a distinct sub-lineage associated with various sources of infection; demonstrated the occurrence of ongoing transmission of COVID-19 within hospitals; and cases of hospital acquired infection. As transmission of COVID-19 in the community occurs, incidence of hospital acquired infection is likely to be higher in the absence of public health measures. Therefore, there is a continuing need to reduce spread of infection at high risks settings by strictly adhering to the infection prevention and control guidance (25). These measures should include, but are not limited to, testing of patients before hospital admission, isolation of infected patients in separate wards, and recommending wearing of masks by visitors and staff when cases are identified (25) .

5. Conclusion

Genomic surveillance and epidemiological investigation based on case interviews and retrospective data collection on an ad hoc basis can be useful to monitor transmission pathways and determine severity of COVID-19 sub-lineages of interest. In this study, we have demonstrated the occurrence of unrecognised hospital acquired infection of SARS-CoV-2. As there remains a risk of transmission in high-risk settings among vulnerable individuals, early detection of cases, and ensuring effective infection prevention and control measures should be prioritised to reduce the burden of the disease.

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7. Appendix

Questionnaire for case interview

I am calling from Queensland Health in relation to your recent COVID-19 illness.

You were infected with a new strain of the virus that caused your illness. There is nothing to worry about and we would just like to interview you to better understand how you acquired the infection.

Is it good to speak to you now? If not when and what time?

- Name
- Date of Birth
- Sex
- Aboriginal and/or Torres Strait Islander status
- Address
- COVID-19 test date
- Admitted to hospital?
- Doctor/Clinic:
- Hospital name:
- Admission date: Discharge date:
- Any antivirals taken (Lagevrio, Paxlovid)
- Vaccination history (doses)

1. How do you think you got the infection?

2. Have you travelled recently? Overseas or interstate? Country/State? If yes. When?

3. When did you develop your first symptom/s?

4. Can you please tell how many members are in your household (live together)?

5. Were your household/ family members infected at the same time or just before or after your illness? If yes, who were infected?

6. Do you know anyone else who visited you and were infected (before or after you were infected)?

7. Did you visit any other hospitals/aged-care facilities/retirement village or attend events just before/after your illness?

If yes, which and when?

Review the answers to questions

8. Do you have anything else to say?

Thank you for your time.

7. Appendix

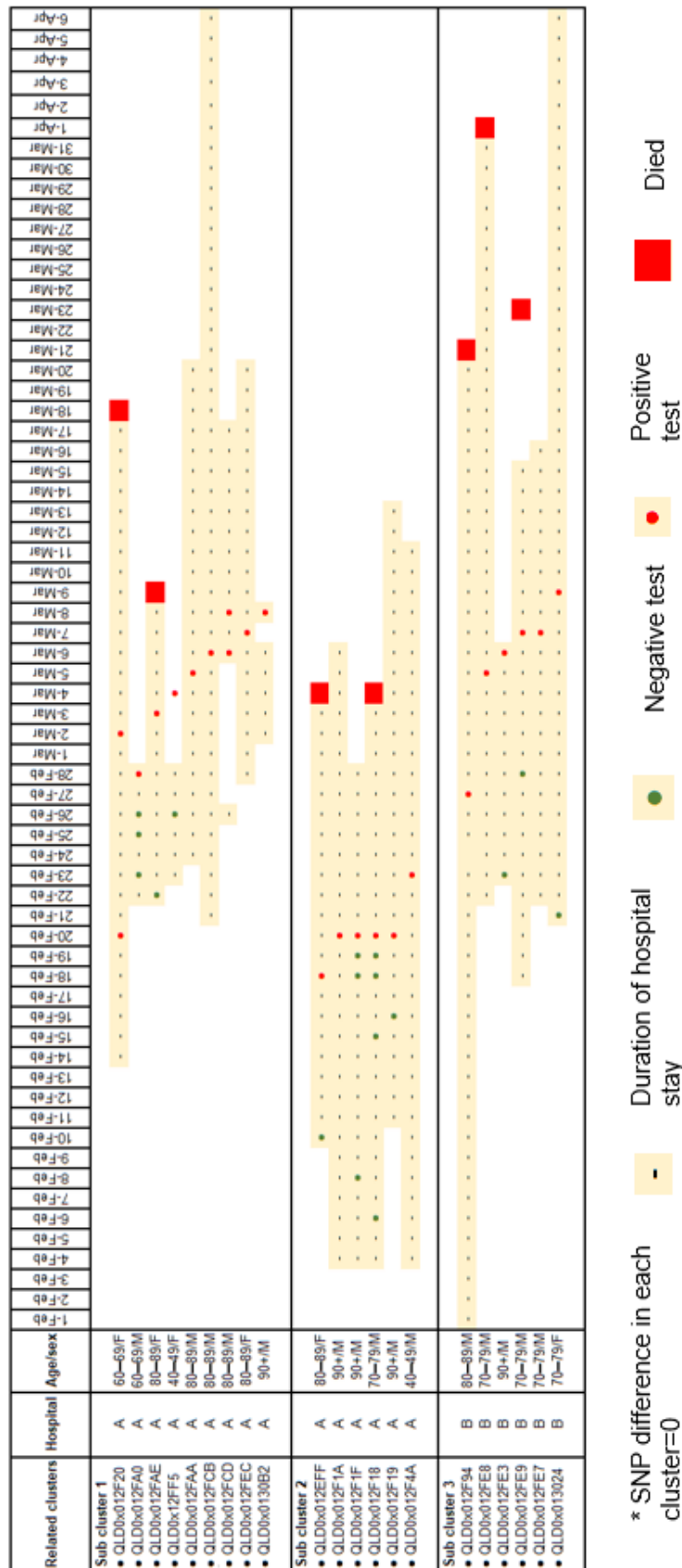


Figure 1. Sub-cluster cases of hospital acquired infections at hospital A and B by specimen collection date, Queensland, 2023

Chapter IV:

Design and conduct an epidemiological study

Influenza epidemiology and vaccine effectiveness following public funding of an influenza vaccine program in Queensland, 2022

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Prologue

During the 2020–2021 COVID-19 pandemic, there were a very few influenza cases notified across Australia. In 2022, with easing of COVID-19 restrictions, an increase in influenza notifications was observed, reaching pre-pandemic level. Free influenza vaccine was made available to all Queensland residents from 24 May to 17 July 2022, aiming to reduce the burden of influenza. This provided an opportunity to estimate influenza vaccine effectiveness among all age groups.

My role

This Chapter demonstrates my competency in designing a research project using a feasible epidemiological study design. I conducted an extensive literature review to understand the context of the proposed project on influenza vaccine effectiveness in Queensland. A strategic search of literature was performed to review the research topic, covering Australian publications in the last ten years (Annex). This demonstrated my ability to conduct targeted literature search, review, and use the peer-reviewed published information to develop a project with a feasible study design. I drafted a concept note which was developed into a proposal after consultation with my supervisors. I drafted applications for submission to Queensland Health Metro North Human Research Ethics Committee and Office of Research and Innovation and obtained recognition of prior approval from the Australian National University Human Research Ethics Committee. I consulted with the Epidemiology and Research Unit and Data Services at the Communicable Diseases Branch regarding data required for the project.

My role and responsibility ranged from project development, management, and collaboration with stakeholders. I was involved in managing, cleaning, and matching of a large dataset. I wrote Stata commands for descriptive and statistical analyses and generated charts, tables, and maps. I discussed the results and findings of the project with my supervisors and other co-investigators for feedback and wrote this Chapter of thesis.

Lessons learned

Undertaking the work for this Chapter gave me an understanding that epidemiological studies are useful in evaluating public health interventions, such as vaccination programs and inform public health policy and practice. I developed an in-depth knowledge of case-control study design and skills in data management from data cleaning, random control selection, and matching with cases for a study. There are challenges in designing appropriate epidemiological studies to estimate vaccine effectiveness. These include access to data on disease of interest and history of vaccination against the disease. I learned that it was crucial to consider

confounding factors and biases in designing studies. The integration of Australian Immunisation Register data with the disease surveillance system data made this study possible and it gave me an understanding of the value and scope of data-linkage. Therefore, this project provided me an opportunity to develop a wide variety of skillsets to successfully demonstrate my competency in conducting epidemiological studies.

Public health impact

Influenza vaccine effectiveness studies are important to monitor and measure how well vaccines work in a real population setting after they are introduced under a funded immunisation program. Such estimates are useful to make recommendations for changes in vaccine composition if required. This study estimated influenza vaccine effectiveness for all age groups of Queensland population to understand impact of the funded vaccination program. It also demonstrated feasibility and value of conducting such studies based on routinely collected, integrated data from different sources.

Acknowledgements

I acknowledge my supervisors for providing an opportunity to develop and demonstrate my competency in designing epidemiological studies. I appreciate their expert guidance for the timely completion of the project. My sincere thanks to Prof. Robert Ware, Prof. Ross Andrews, and Ms. Dharshi Thangarajah for valuable feedback and statistical support in analysing the data. Thanks to Mr. Ramim Sourjah for integrating the influenza and COVID-19 test notification datasets with the vaccination data from the Australian Immunisation Register. I also thank the Epidemiology and Research Unit and Data Services at the Communicable Diseases Branch for providing insights into data fields and extracting the data.

Abstract

Background: Estimation of disease burden due to influenza is important to determine the seasonal threat, assist in the development of preparedness strategies, and for the effective implementation of prevention and control measures. Influenza vaccination is one of the important interventions to reduce the burden related to influenza infection. This study aimed to understand influenza epidemiology for the year 2022 compared to the previous years (2017–2021) in Queensland and estimate influenza vaccine effectiveness (VE) among all age groups after the introduction of publicly funded influenza vaccination program in 2022 in Queensland.

Methods: The study involved a descriptive analysis of influenza notifications in Queensland from 2017 to 2022. A case-control study design was used to estimate VE including laboratory confirmed influenza cases and negative COVID-19 test controls from 1 May 2022 to 31 October 2022. Data on cases and controls were obtained from the Notifiable Conditions System. Influenza vaccination status was available from the Australian Immunisation Register. Cases and controls were matched on age, postcode, and specimen collection dates. Hospitalised influenza cases were also matched to controls. Conditional logistic regression was used to calculate crude odds ratio (OR) and VE against laboratory confirmed influenza and influenza associated hospitalisation. OR was adjusted by sex to calculate adjusted OR and adjusted VE (VE_{adj}). The estimates were stratified by age groups, influenza virus types, and for children aged <9 years by vaccine dose completeness and number of doses.

Results: In 2022, an increase in the inter-seasonal influenza activity was observed with the early commencement of seasonal influenza. Overall, VE_{adj} against laboratory confirmed influenza was 39% (95% CI: 37–41) and was highest for children aged 30 months–<5 years (61%, 95% CI: 49–70) and lowest for adults aged ≥ 65 years (24%, 95% CI: 17–30). The point estimate for children <9 years old was higher among those completely vaccinated (55%, 95% CI: 49–61) compared to incompletely vaccinated (18%, 95% CI: -14–40). Overall, VE_{adj} against hospitalisation due to influenza was 54% (95% CI: 48–59) and highest for children aged 5 years–<9 years (84%, 95% CI: 48–95). Likewise, protection against hospitalisation was higher for complete dose (67%, 95% CI: 39–82) recipients compared to incomplete dose recipients (18%, 95% CI: -142–72) among children <9 years of age.

Conclusion: In Queensland, the influenza season started earlier in 2022 than the previous five years (2017–2021). VE against influenza notifications varied across age groups, and was most effective among children who received a complete dose schedule. Higher VE against hospitalisation demonstrates better vaccine protection against a more severe influenza infection outcome.

1. Background

Influenza is a respiratory tract infection caused by influenza viruses (family *Orthomyxoviridae*) type A, B, C, and D (1). The most common influenza viruses to cause human illnesses are influenza viruses types A and B (2). Influenza A viruses have different subtypes based on the surface proteins haemagglutinin (H) and neuraminidase (N) (H1–H18 and N1–N11) with more than 130 subtype combinations (2, 3). Influenza virus type B is classified into two lineages: B/Yamagata and B/Victoria (2, 3). The virus is transmitted through respiratory droplets or contact with an infected person or surface (4). The incubation period ranges from 1–4 days and viral shedding occurs from -1 to 5–7 days after the onset of symptoms (lasts for a week or more) (5, 6). Influenza is characterised by systemic (fever, chills, headache), respiratory (runny nose, sneezing, cough, sore throat), musculoskeletal (body aches, fatigue), and gastrointestinal (vomiting, diarrhoea) symptoms (5, 6). Complications following influenza infection can involve nervous, cardiac, respiratory, and musculoskeletal systems and may require hospitalisation, or where severe enough, can lead to chronic illness and occasionally, death (6).

The populations at most risk of severe outcomes following infection includes children aged <5 years, adults ≥65 years old, pregnant women, postpartum women (up to 2 weeks after delivery), and individuals with chronic medical conditions (asthma, neurologic conditions, blood disorders, lung disease, diabetes, kidney disease, metabolic disorders, immunocompromised, obesity) (7). Influenza causes significant morbidity and mortality, which result in negative socio-economic impacts (8). Seasonal influenza epidemics are estimated to infect ~20% of the world's population causing 290,000–650,000 deaths, annually (9). Estimation of disease burden due to influenza is important to determine the seasonal threat, assist in the development of preparedness strategies, and for the effective implementation of prevention and control measures (10). Laboratory confirmed influenza is a nationally notifiable condition in Australia (11). In 2022, there were 225,332 influenza notifications (laboratory confirmed) and 308 influenza associated deaths reported to the National Notifiable Diseases Surveillance System (12). As of 11 September 2022, there were 42,338 influenza notifications (type A: 42,268 (99.84%) and type B: 70 (0.16%)) in Queensland with the highest notification rate among children aged 5–9 years (13).

Influenza vaccination is an important intervention to reduce morbidity and mortality related to influenza infection (14). A meta-analysis estimated influenza vaccine effectiveness (VE) of 39% for outpatient or emergency influenza care visits, 57% for hospitalisation among those aged 6 months–18 years old and 25% for outpatient visits and 14% for hospitalisation among those aged ≥65 years old (15). Vaccination can provide indirect protection to unvaccinated

individuals through ‘herd protection’ (16). Studies have shown that mass immunisation of children with influenza vaccine reduces influenza-related illness and mortality in unvaccinated elderly population (17, 18). Therefore, influenza vaccination is known to reduce risk of severe disease among high-risk population and prevent further transmission.

Influenza vaccine is recommended every year for everyone in Australia (19). The National Immunisation Program (NIP) funds influenza vaccines for population at risk including children 6 months to <5 years old, all Aboriginal and Torres Strait Islander people (≥6 months), individuals 65 years and older, and pregnant women (19). In Queensland, initial distribution of NIP funded influenza vaccine commenced on 4 April 2022 (personal communication, Thomas Clayton, Immunisation Program, Communicable Diseases Branch, Queensland Health) and free influenza vaccine was made available to all residents from 24 May 2022 until 17 July 2022 under the Queensland Government’s free influenza vaccination campaign (20-22). The World Health Organization (WHO) makes an annual hemisphere-specific recommendation on influenza vaccine composition based on the epidemiology, laboratory (antigenic and genetic characteristics of influenza isolates), clinical studies, and the availability of flu vaccine viruses (23). Only quadrivalent vaccines were used in Australia in 2022 with each vaccine containing components of four influenza virus strains – two influenza A subtypes (H3 and H1) and two influenza B lineages (Victoria and Yamagata lineages) (24). At the end of the 2022 season, of the 2,570 samples referred to the WHO Collaborating Centre (WHOCC), 92.4% of influenza A(H1N1) isolates, 94.5% of influenza A(H3N2) isolates, and all six influenza B/Victoria isolates, were characterised as antigenically similar to the corresponding vaccine components (25). Influenza case numbers were low during the COVID-19 pandemic years and reduced the number of influenza virus available for characterisation (26). This could have impacted the match between the vaccine composition and circulating virus in 2022, however, from the WHOCC data, vaccine and circulating strain match in 2022 was very good.

Influenza vaccine is recommended before the influenza season starts, which in south-east Queensland is typically around May and is considered finished by October (peak between June–September each year) (27, 28). Optimal protection extends to 3–4 months following vaccination (28). As influenza viruses undergo genetic mutation and reassortment, circulating virus may not match well to vaccine formulation (29). Hence, estimated VE from previous years may not remain same for the updated vaccines and for the modified circulating viruses (30). Annual influenza VE estimates are useful in determining protective effect of vaccines; conducting further investigations to improve composition; developing strategies to respond to vaccine failures; and managing risks (30). There has been limited study on influenza VE in Queensland, with a previous study reporting effectiveness only among children <5 years old

(31). With this study I aimed to understand the epidemiology of influenza and estimate VE across all ages in Queensland after the introduction of funded influenza vaccine program.

2. Methods

2.1. Study design

The study involved two components: a descriptive analysis of influenza notifications in Queensland for the year 2022 and comparison with the previous years (2017–2021). It also involved case-control study used to estimate influenza VE in Queensland in 2022.

Case definitions

In Queensland, influenza confirmed cases are notified based only on laboratory definitive evidence (32). The laboratory definitive evidence includes either isolation of influenza virus by culture or detection of the virus by nucleic acid testing or detection of antigen or IgG seroconversion or rise in antibody titre against the virus (32). Cases are electronically notified by public and private pathology laboratories to the Queensland Health Notifiable Conditions System (NoCS).

2.2. Source of data

Epidemiology and seasonal trend

Data on laboratory confirmed cases of influenza were obtained from NoCS for the study period 2017–2022 (data extracted on 13 January 2023). Queensland Hospital Admitted Patient Data Collection data were routinely integrated on a quarterly basis with NoCS, to capture influenza related hospitalisation. Age-specific mid-year population data of Queensland were obtained from the Australian Bureau of Statistics to calculate notification rates of influenza (33).

Vaccine effectiveness

Cases

Influenza confirmed cases with specimen collection dates from 1 May 2022 to 31 October 2022 were included for the VE study (data extracted from NoCS on 23 May 2023). The cases were linked to Queensland population registered in the Australian Immunisation Register (AIR) to obtain history of influenza vaccination (January 2017–May 2023) and COVID-19 vaccination (January 2021–May 2023). Vaccination status was recorded within NoCS with the routine integration of jurisdictional AIR data held by Queensland Health.

Controls

Controls included individuals who had a COVID-19 test reported between 1 May 2022 to 31 October 2022 (data extracted from NoCS on 23 May 2023). All COVID-19 test notifications including positive and negative are electronically received by NoCS. These test notifications were also linked to history of influenza vaccination (January 2017–May 2023) and COVID-19 vaccination (January 2021–May 2023). Individuals with a COVID-19 test were used as controls to reduce selection bias due to community level variations such as health seeking behaviour, access to health care facilities for treatment, testing and vaccine uptake, and health risk behaviours. Primary analysis for VE included individuals with a negative COVID-19 test during the study period. For the individuals with multiple negative tests, only the first test during the study period was included. Individuals with any positive COVID-19 test during the period were excluded to reduce selection bias due to correlation of receipt of both COVID-19 and influenza vaccination (34, 35). As a secondary sensitivity analysis, I included individuals with positive and negative COVID-19 tests during the study period. For individuals with both positive and negative tests, the first positive test was included in the sensitivity analysis.

Data linkage

Linkage was performed by the Data Services team, Communicable Diseases Branch, Queensland Health. Linkage keys were generated based on the matching criteria in the following order between NoCS and AIR. If matching with the first linkage key was unsuccessful, then the second linkage key was used and so on.

1. Medicare number (8 digits) AND first name AND date of birth
2. Last name AND first name AND date of birth AND postcode
3. Medicare number (8 digits) AND similar string sounds of first name AND similar string sounds of last name AND date of birth
4. Similar string sounds of first name AND date of birth AND last name AND postcode

Exclusion criteria

Influenza and COVID-19 tests duplicates with the same notification dates, notifications with interstate or overseas residence and with postcodes outside Queensland, unknown sex, and unknown age were excluded. Cases and controls were restricted to children aged at least 6 months and 14 days (≥ 196 days) at specimen collection date to account for 14 days required to confer active immunity due to influenza vaccine. Therefore, individuals < 196 days were excluded. Individuals of 9 years and older age, who received two or more doses of vaccine in

2022 were considered invalid and excluded from analysis. COVID-19 test controls who were notified as influenza cases were also excluded from the control population.

Vaccination status

Cases and controls were considered vaccinated if influenza vaccine/s were received in 2022 during the study period. Cases who received influenza vaccine <14 days prior to the specimen collection date were considered unvaccinated. Therefore, for the case to be considered vaccinated, the difference between specimen collection date and vaccination date needed to be ≥ 14 days. The same criteria were applied to the controls using the specimen collection date of their matched cases.

Vaccination doses and completeness

Doses of influenza vaccine received in 2022 by children 6 months–<9 years of age were determined. A second dose was considered to be valid if received ≥ 28 days after the first dose. A child who received a second dose <28 days after the first dose was considered to have received a single dose. Children who received second dose vaccine <14 days prior to the specimen collection date were also considered to have received a single dose.

Vaccine completeness status was determined as per the Australian Immunisation Handbook dosage recommendations for children <9 years old (28). Complete status referred to receipt of two doses in 2022 with or without prior doses, OR one dose in 2022 and one or more dose prior to 2022. Vaccination history from the AIR was available since 2017 for participants in this study. Incomplete dosing referred to recipient of only one dose in 2022 and no prior dose.

Matching

Controls were matched to cases on postcode, specimen collection dates (± 14 days of COVID-19 test specimen collection date from cases' specimen collection date), and age. The age matching criteria were as follows, with controls drawn from the same age groups as their case (Table 1).

Table 1. Case and control age matching criteria

Age groups of case and controls	Difference in days
6 months–<30 months	± 14 days
30 months–<5 years	± 14 days
5 years–<9 years	± 60 days
9 years–<20 years	± 180 days
20 years–<65 years	± 365 days
≥ 65 years	± 365 days

Matched controls with same date of birth and sex as their respective matched cases were excluded to avoid chances of a case being their own control. Controls who matched to multiple cases were randomly assigned to one case. The maximum number of controls per case was restricted to 10 (range 1–10 controls per case). When more than 10 controls matched to an individual case, 10 controls were randomly selected from all available controls.

2.3. Data analysis

2.3.1. Descriptive epidemiology

The trend of influenza notifications was determined as counts of notified cases by weeks (International Organisation for Standardisation (ISO) 8601 Standard weeks) of episode dates (earliest of onset and specimen collection dates) from 2017 to 2022. Cases were described by sex and Aboriginal and Torres Strait Islander status. Incidence rate of notification as rates per 100,000 population by year and age groups were calculated. Seasonal (weeks 22–44) and inter-seasonal periods (weeks 45–21) were based on historical Queensland influenza activity (36). The distribution was examined for the seasonal and inter-seasonal periods and the ratio of seasonal and inter-seasonal notifications calculated by year and geographical regions (Southern, Central and Tropical). The cases were categorised into regions based on the notifying Hospital and Health Services (HHSs) and Bureau of Meteorology climate zones (37–39).

Influenza activity was determined for each year by aligning weekly notification rates with an epidemic threshold (40). In this study, the thresholds were estimated for seasonal and inter-seasonal periods using moving endemic model (41–43) and for this calculation, data from the 53rd week were excluded. Epidemic thresholds were also used as medium thresholds (as medium thresholds were less than epidemic thresholds). The analysis was performed using RStudio 2023.03.0 (Posit Software, Boston, Massachusetts), the R Language (v4.0) and ‘MEM’ R Package (41). Data management and analysis were performed using Microsoft Excel Version 2202 (Microsoft, Redmond, Washington) and Stata version SE 16.1 (StataCorp, College Station, TX). Cases notified in 2022 were mapped based on the location of the HHSs using QGIS 3.28 (QGIS Association) (44).

2.3.2. Vaccine effectiveness against laboratory confirmed influenza

Crude odds ratio (OR) was estimated as ratio of the odds of exposure (vaccination) among influenza cases and odds of exposure (vaccination) among controls (COVID-19 test negative).

$$\text{OR} = \frac{\text{Odds of vaccination among cases}}{\text{Odds of vaccination among controls}} = \frac{\frac{\text{Number of cases vaccinated}}{\text{Number of cases unvaccinated}}}{\frac{\text{Number of controls vaccinated}}{\text{Number of controls unvaccinated}}}$$

OR was calculated using conditional logistic regression (as controls were matched with cases). OR was adjusted for sex in the regression analysis to calculate adjusted OR and estimate adjusted VE (VE_{adj}). Crude VE, VE_{adj}, and their confidence intervals (CI) were calculated for any dose received in 2022 for all age groups and vaccine completeness (no vaccine, complete, and incomplete) and vaccine doses received in 2022 (none, one and two doses) for children <9 years old. The estimates were also stratified by age group (6 months–<30 months, 30 months–<5 years, 5 years–<9 years, 9 years–<20 years, 20 years–<65 years, ≥65 years). *P*-value for differences in overall vaccine uptake between cases and controls were calculated using Pearson's Chi-squared test. Data analyses were performed using Stata version SE 16.1 (StataCorp, College Station, TX, USA) and Microsoft Excel Version 2202 (Microsoft, Redmond, Washington).

2.3.3. Vaccine effectiveness against influenza associated hospitalisation

Influenza cases recorded as being hospitalised in NoCS were included for the estimation of VE against hospitalisation. Cases were matched to controls similarly to the criteria used for VE against laboratory confirmed influenza. VE and VE_{adj} were estimated by age groups, dose completeness, and number of doses received in 2022.

2.3.4. Sensitivity analysis

Sensitivity analysis using statistical area instead of postcode was performed by matching on statistical area 2 (SA2) where available, age, and specimen collection date. SA2 was determined based on statistical area 1 (SA1) recorded in NoCS and cases and controls with missing SA1 were excluded prior to matching.

A sensitivity analysis was also performed including individuals with both positive and negative COVID-19 tests as controls and matched on postcode, age, and specimen collection date.

2.4. Ethics and other approvals

Ethics approval for this project was obtained from Queensland Health Metro North Human Research Ethics Committee B (HREC/2022/MNHB/91287). This ethics approval was recognised by the Australian National University Human Research Ethics Committee. Queensland Health Communicable Diseases Branch Data Custodian approval and Public Health Act approval were also provided for the study.

3. Results

3.1. Influenza notifications and demographic characteristics, 2017–2022

A total of 45,311 influenza cases (confirmed by nucleic acid testing: $n=43,862$, 96%) were notified in 2022, which was 33% and 20% lower compared to 2019 ($n=68,151$) and 2017 ($n=56,614$), respectively. However, it was 188% higher than the cases notified in 2018 ($n=15,705$). Comparatively, smaller numbers of cases were notified during the COVID-19 pandemic years, 2020 ($n=6,047$) and 2021 ($n=301$). Influenza season commenced in April–May 2022 and the notifications peaked in weeks 23–24 (June) compared to 33–34 weeks (August) in 2017 and 2019 (Figure 1).

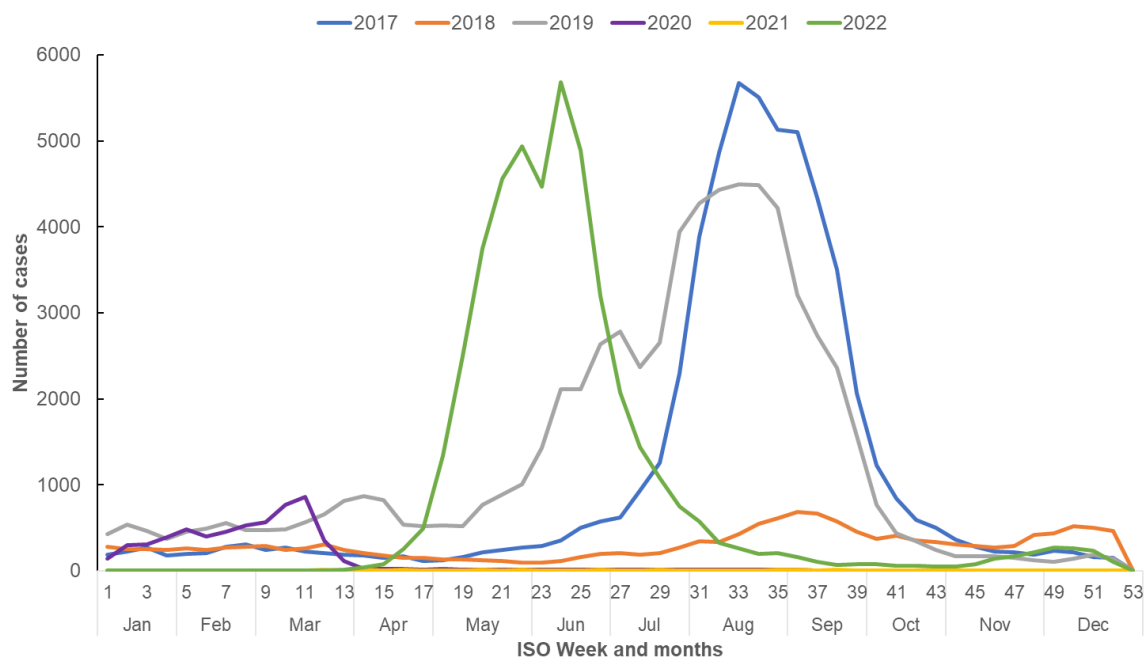


Figure 1. Total influenza notifications by month and week of episode date, Queensland, 2017–2022

Overall, the proportion of cases that were female (54%) was higher compared to males (46%), with similar proportions each year. The notification rates were higher among children <9 years old and older age groups (>70 years) (Figure 2). Aboriginal and Torres Strait Islander people represented 10% of notified cases in 2022 and 5–7% of all the cases notified in 2017–2021.

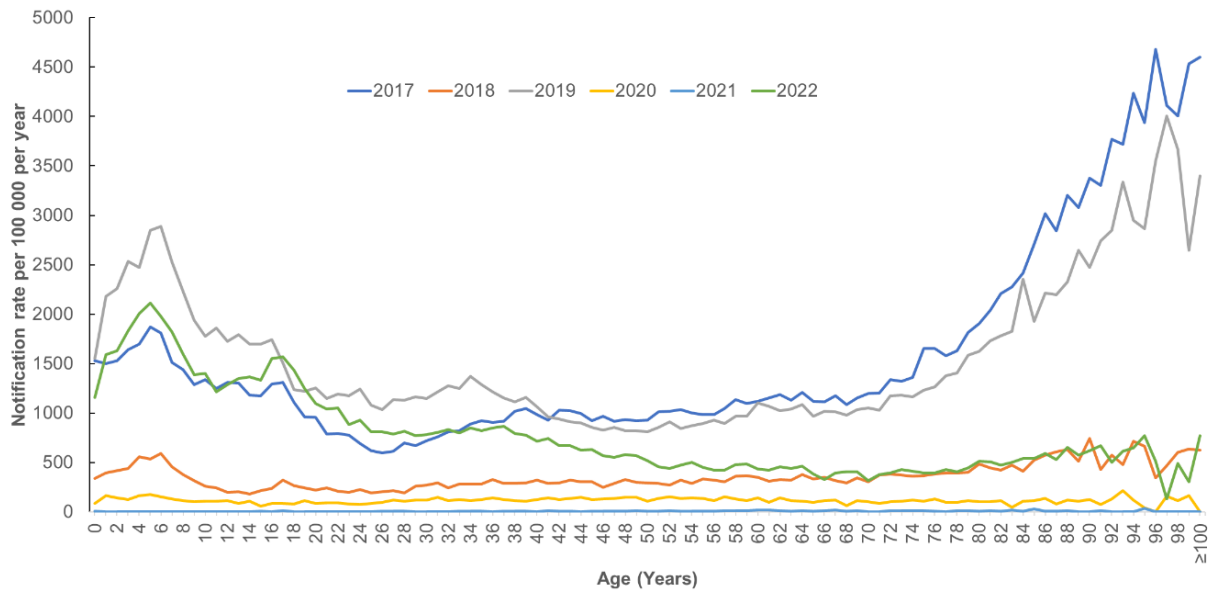


Figure 2. Influenza notification rate by year and age, Queensland, 2017–2022

3.2. Seasonal and inter-seasonal epidemiology, 2017–2022

During the study period (2017–2022), 24.8% (47,661/192,129) of all the cases occurred during the inter-seasonal period (weeks 45–21) (Table 2). The proportion of cases occurring during the inter-seasonal period was higher in 2018 (49.6%), 2020 (96.4%), and 2021 (55.5%). The overall proportion of cases during the inter-seasonal period was also higher (42%) in the tropical region compared to the central (22.5%) and southern (21.6%) regions.

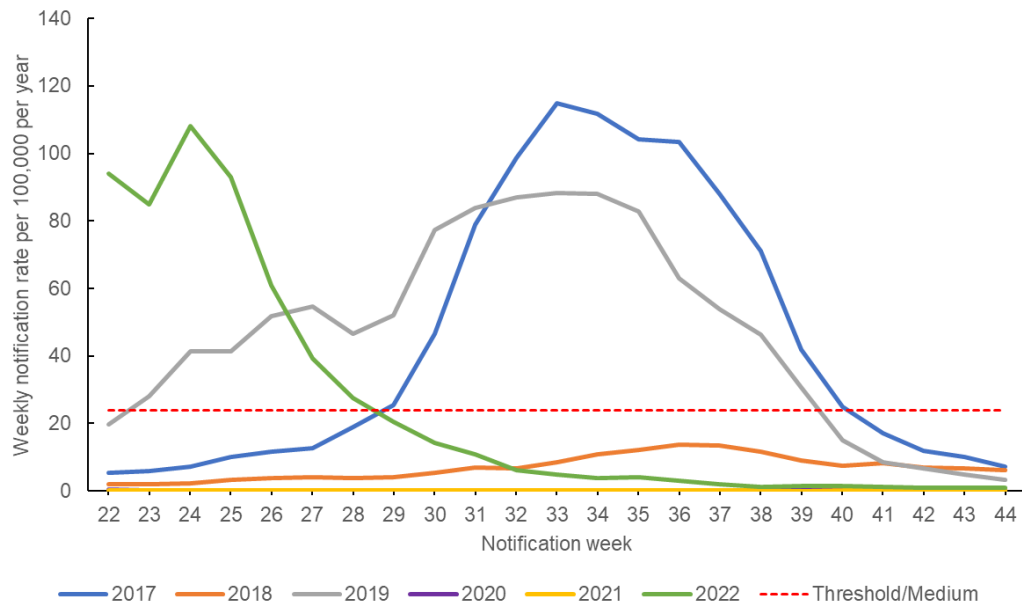
Table 2. Seasonal (S) and inter-seasonal (IS) influenza notifications (n), proportions (%), and ratios (R) by year and regions, Queensland, 2017–2022

Characteristics		2017	2018	2019	2020	2021	2022	All
Cases	S	50,641 (89.4%)	7,920 (50.4%)	54,763 (80.4%)	216 (3.6%)	134 (44.5%)	30,794 (68%)	144,468 (75.2%)
	IS	5,973 (10.6%)	7,785 (49.6%)	13,388 (19.6%)	5,831 (96.4%)	167 (55.5%)	14,517 (32%)	47,661 (24.8%)
	R	0.12	0.98	0.24	27	1.25	0.47	0.33
Regions								
Central	S	18,529 (89%)	3,342 (52.5%)	22,040 (83.9%)	62 (2.7%)	46 (40.7%)	11,090 (72.5%)	55,109 (77.5%)
	IS	2,282 (11%)	3,020 (47.5%)	4,239 (16.1%)	2,211 (97.3%)	67 (59.3%)	4,210 (27.5%)	16,029 (22.5%)
	R	0.12	0.90	0.19	35.66	1.46	0.38	0.29
Southern	S	26,142 (98.4%)	3,413 (51.4%)	27,374 (84.8%)	116 (4.2%)	71 (47.6%)	16,183 (70.1%)	73,299 (78.4%)
	IS	2,425 (1.6%)	3,231 (48.6%)	4,891 (15.2%)	2,652 (95.8%)	78 (52.4%)	6,901 (29.9%)	20,178 (21.6%)
	R	0.09	0.95	0.18	22.86	1.10	0.43	0.28
Tropical	S	5,970 (82.5%)	1,165 (43.2%)	5,349 (55.7%)	38 (3.8%)	15 (4.1%)	2,759 (47.2%)	15,296 (57.9%)
	IS	1,266 (17.5%)	1,534 (56.8%)	4,258 (44.3%)	968 (96.2%)	22 (95.9%)	3,091 (52.8%)	11,139 (42.1%)
	R	0.21	1.32	0.80	25.47	1.47	1.12	0.73

S: Seasonal (weeks 22–44); IS: Inter-seasonal (weeks 45–21); R: Ratio (Inter-seasonal/seasonal)

The weekly notification rates were above the estimated threshold for 2017 (weeks 29–40), 2019 (weeks 23–39), and 2022 (weeks 22–28) during the seasonal period (Figure 3A). The rates were above threshold for 2017/2018 (weeks 47–52), 2018/2019 (weeks 1–21), and 2019/2020 (weeks 4–12) and high for 2021/2022 (weeks 17–21) during the inter-seasonal period (Figure 3B). ‘No activity’ was observed for influenza notifications in 2020/2021.

A)



(B)

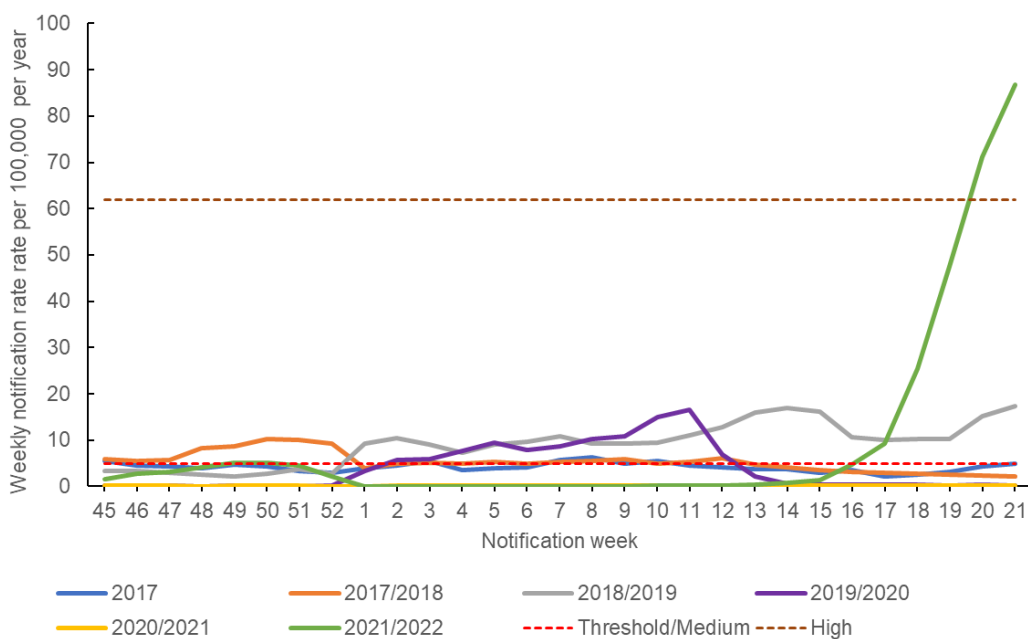


Figure 3. Weekly influenza notification rates per 100,000 population per year, 2017–2022, Queensland, (A) Seasonal period (B) Inter-seasonal period

A majority of the cases in 2022 were infected with influenza A (99.58%, $n=45,094$) followed by influenza B (0.37%, $n=170$), and dual infections with both A and B (0.04%, $n=16$). In previous years (2017–2021), the proportion of cases infected with influenza A ranged from 66–88% and with B (11–33%) (Figure 4). In 2022, of the cases with influenza A subtypes known ($n=3,883$), 810 were Influenza A H1, 3,059 were influenza A H3, and 14 were influenza A H1 and H3.

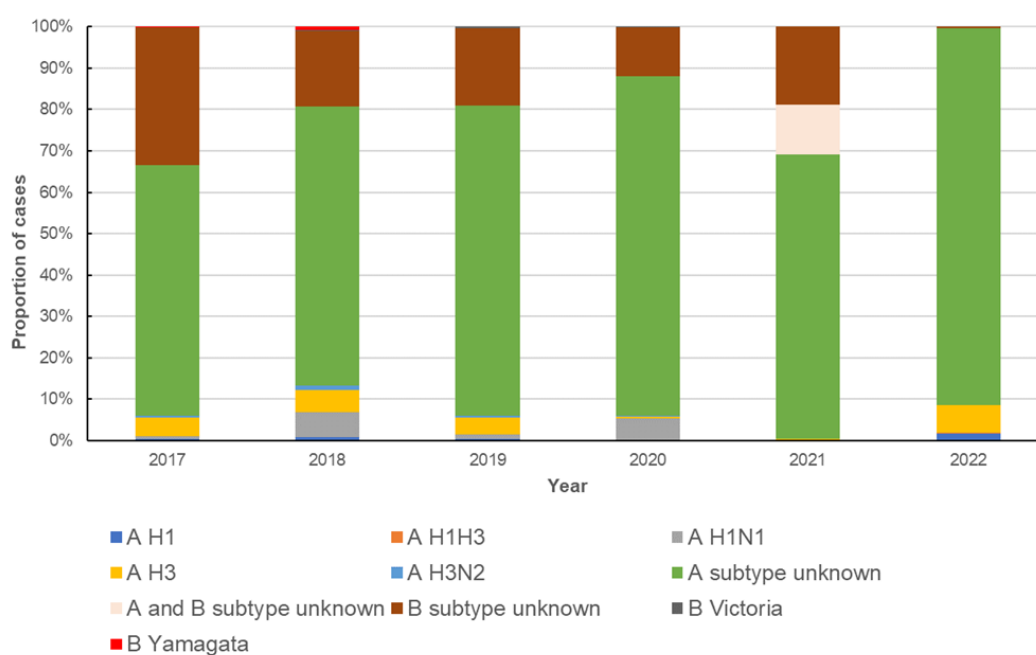


Figure 4. Proportion of Influenza notification by year and influenza sub-types, Queensland, 2017–2022

3.3. Hospitalisation due to influenza, 2022

In 2022, there were 3,917 (8.6%) cases recorded as hospitalised due to influenza. The age groups with the highest proportion of notified cases who were hospitalised was the 20–<65 (41%) and ≥65 (29.3%) year olds (Table 3). Of the hospitalised cases, 20% (n=774) occurred in children <9 years old.

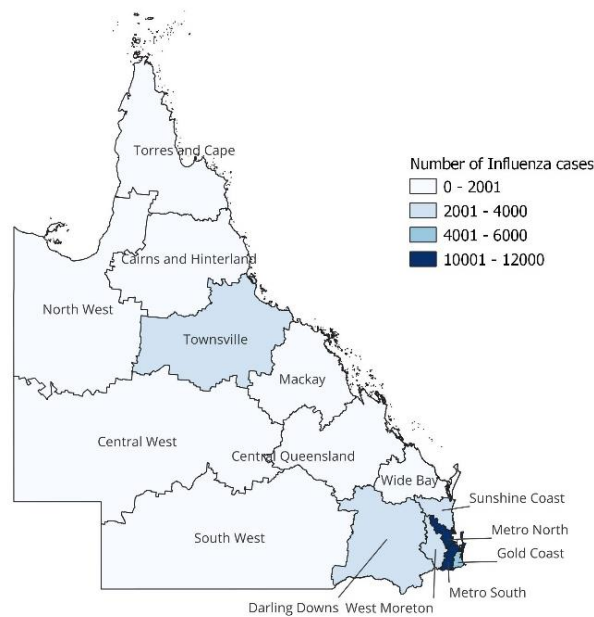
Table 3. Cases hospitalised due to influenza, 2022

Age groups	Cases n (%)	Cumulative %
6 months–<30 months	317 (8.1%)	8
30 months–<5 years	243 (6.2%)	14
5 years–<9 years	214 (5.5%)	20
≥9 years–<20 years	387 (9.9%)	30
20 years–<65 years	1,606 (41%)	71
≥65 years	1,150 (29.3%)	100

3.4. Influenza notifications and Hospital and Health Services, 2022

In 2022, the highest proportion of laboratory confirmed cases were notified from Metro South (25.1%, n=11,097) and Metro North (23.58%, n=10,430) with the notification rate of 907 and 980 per 100,000 per year, respectively (Figure 5A, 5B). However, the notification rates were higher in North West (2,153 per 100,000 per year, n=568), Torres and Cape (1,850 per 100,000 per year, n=496), and South West (1,816 per 100,000 per year, n=421) (Figure 5B).

(A)



(B)

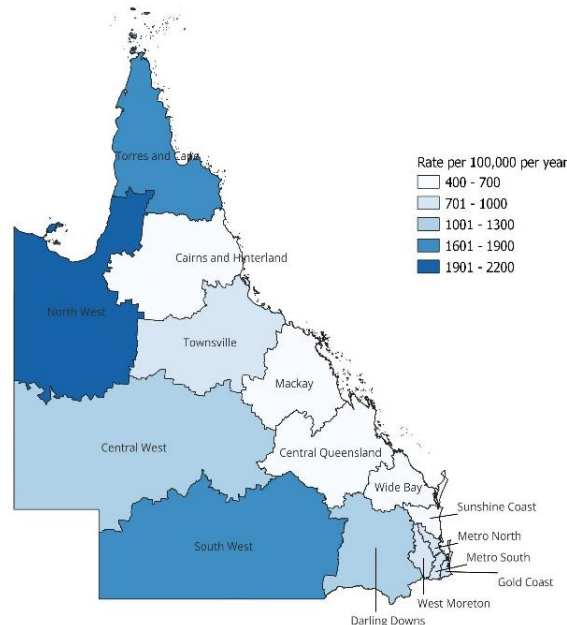


Figure 5. Influenza notifications by Hospital and Health Services, Queensland, 2022 (A) Number of cases (B) Rate per 100,000 population per year

3.5. Influenza vaccine effectiveness against laboratory confirmed influenza

3.5.1. Case-control matching

There were 43,029 influenza notifications in NoCS based on specimen collection date from 1 May 2022 to 31 October 2022 (Figure 6). Of these, a total of 1,462 notifications were excluded, including children of age <196 days (n=275) and those who received two doses of vaccine in 2022 for those aged ≥ 9 years old (n=88).

During the same period, 1,509,567 COVID-19 tests were performed. A total of 992,865 COVID-19 tests were excluded during the study period: those with an unknown test result (n=5,097), all tests of positive COVID-19 tested individuals (n=687,006), negative tests beyond the initial negative test (n=182,115), and tests of individuals who were notified as influenza cases (n=33,783). Children aged <196 days at the time of specimen collection (n=8,026) and individuals aged 9 years and older with two or more doses of vaccine in 2022 (n=1,825) were also excluded.

Influenza cases (n=41,567) and COVID-19 negative controls (n=516,702) were available for matching on age, postcode, and specimen collection dates. Of the 177,980 controls matched to 36,737 cases, 96,490 controls matched to more than one case, and were subsequently randomly assigned to match one case. After randomly selecting a maximum of 10 controls for 4,095 cases where there were more than 10 initial matches, a total of matched 154,184 controls and 34,177 cases were included in the analysis for estimation of VE. Of these, 14% of the cases were assigned 10 controls and 67% had 1–5 controls per case (Table 4).

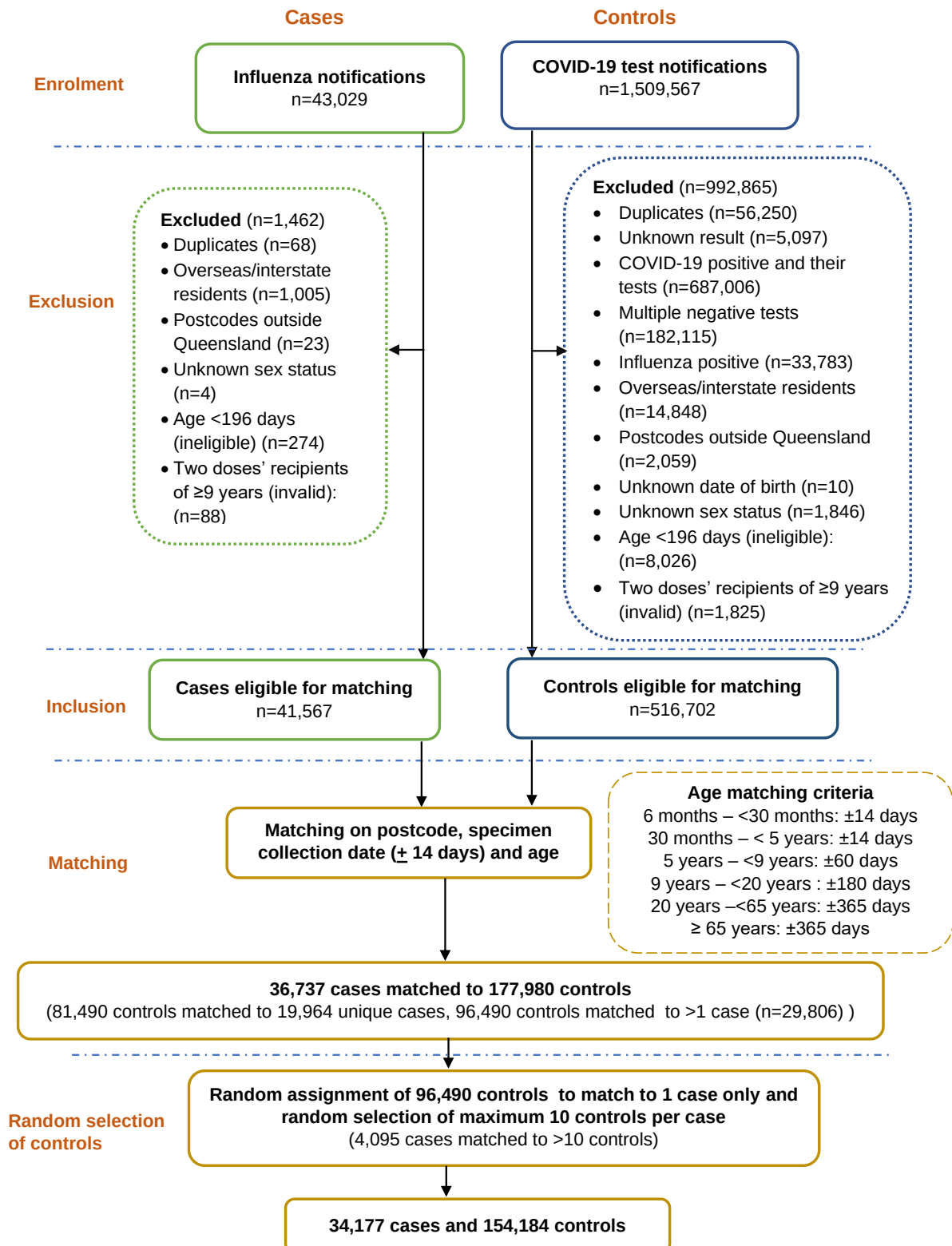


Figure 6. Case and control enrolment and matching on age, postcode, and specimen collection for VE estimates against laboratory confirmed influenza, 1 May 2022–31 October 2022

Table 4. Frequency of controls matched per case

Matched controls per case	Cases (n)	Cumulative %
1	6,787 (19.9)	20
2	5,465 (16)	36
3	4,399 (12.9)	49
4	3,468 (10.2)	59
5	2,696 (8.0)	67
6	2,112 (6.2)	73
7	1,791 (5.2)	78
8	1,419 (4.2)	82
9	1,121 (3.3)	86
10	4,919 (14.4)	100
Total	34,177 (100)	

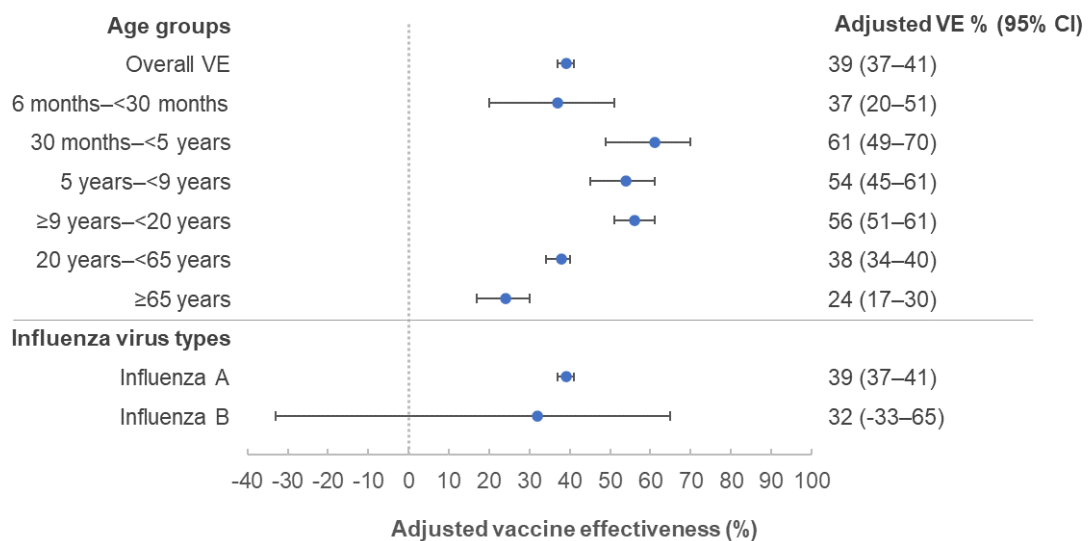
3.5.2. Estimates of Influenza vaccine effectiveness

In 2022, the overall VE for receipt of any influenza vaccine preventing influenza notification among Queensland residents was 39% (95% CI 36–41) (Table 5). Influenza vaccine uptake was higher among the controls (25.2%) compared to the cases (15.4%) ($P < 0.001$). The estimate was similar after adjusting for sex (VE_{adj}) (Figure 7). When stratified by age group, VE_{adj} was highest for 30 months–<5 years (61%, 95% CI: 49–70) and lowest for ≥ 65 years old (24%, 95% CI: 17–30). The estimates were higher than 50% for those 30 months–<20 years old. The point estimate for VE_{adj} against influenza A (39%, 95% CI 37–41) was higher than for influenza B (32%, 95% CI -33–65).

Table 5. Estimates of vaccine effectiveness by vaccination status, age groups, and influenza virus types, Queensland, 2022

	Case n (%)	Control n (%)	Crude OR (95% CI)	Crude VE % (95% CI)
Overall				
Not vaccinated	28,907 (84.6)	115,414 (74.8)	Ref.	Ref.
Vaccinated	5,270 (15.4)	38,770 (25.2)	0.61 (0.59–0.64)	39 (36–41)
6 months–<30 months				
Not vaccinated	1,032 (90.6)	2,371 (86.5)	Ref.	Ref.
Vaccinated	107 (9.4)	370 (13.5)	0.63 (0.49–0.80)	37 (20–51)
30 months–<5 years				
Not vaccinated	1,272 (93.1)	2,108 (85.8)	Ref.	Ref.
Vaccinated	95 (6.9)	350 (14.2)	0.39 (0.30–0.51)	61 (49–70)
5 years–<9 years				
Not vaccinated	2,917 (93.5)	5,985 (87.7)	Ref.	Ref.
Vaccinated	201 (6.5)	838 (12.3)	0.46 (0.39–0.55)	54 (45–61)
9 years–<20 years				
Not vaccinated	7,216 (94.8)	20,156 (88.5)	Ref.	Ref.
Vaccinated	397 (5.2)	2,626 (11.5)	0.44 (0.39–0.49)	56 (51–61)
20 years–<65 years				
Not vaccinated	14822 (82.6)	76,180 (75.2)	Ref.	Ref.
Vaccinated	3,122 (17.4)	25,127 (24.8)	0.63 (0.61–0.66)	37 (34–39)
≥65 years				
Not vaccinated	1648 (55)	8,614 (47.7)	Ref.	Ref.
Vaccinated	1348 (45)	9,459 (52.3)	0.77 (0.70–0.83)	23 (17–30)
Influenza virus types				
Influenza A				
Not vaccinated	24,810 (84.6)	115,511 (74.9)	Ref.	Ref.
Vaccinated	5,251 (15.4)	38,789 (24.1)	0.61 (0.59–0.64)	39 (36–41)
Influenza B				
Not vaccinated	47 (72.3)	144,274 (76.6)	Ref.	Ref.
Vaccinated	18 (27.7)	44,022 (23.4)	0.66 (0.34–1.29)	34 (-29–66)

VE: Vaccine effectiveness; Ref.: Reference group



* Adjusted by sex

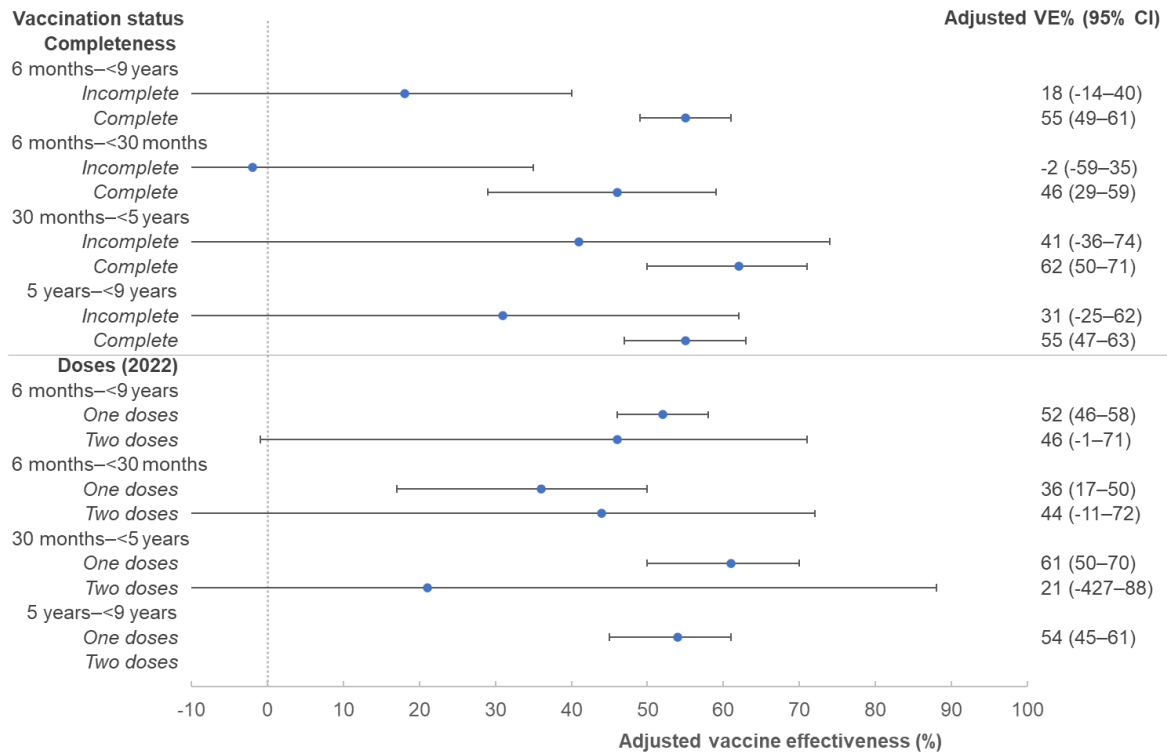
Figure 7. Adjusted VE stratified by age group and influenza virus type

Assessing VE among children 6 months–<9 years old by vaccination doses received in 2022 and in prior years, the point estimate for VE and VE_{adj} was higher for children who were completely vaccinated (55%, 95% CI:49–61) compared to incompletely vaccinated (18%, 95% CI -14–40) (Table 6, Figure 8). VE_{adj} by completeness was highest among 30 months–<5 years, who received complete doses (62%, 95% CI: 50–71) compared to incomplete dose recipients (41%, 95% CI -36–74). Complete doses conferred better protection compared to incomplete doses across all age groups of children. The point estimate of effectiveness of two doses received in 2022 compared to a single dose was higher among 6 months–<30 months old.

Table 6. Estimates of vaccine effectiveness by vaccine completeness and doses among children, Queensland, 2022

	Case n (%)	Control n (%)	Crude OR (95% CI)	Crude VE % (95% CI)
Vaccine completeness				
6 months–<9 years				
Not vaccinated	5,221 (92.8)	10,464 (87.1)	Ref.	Ref.
Incomplete	61 (1.1)	137 (1.1)	0.82 (0.60–1.14)	18 (-14–40)
Complete	342 (6.1)	1,421 (11.8)	0.45 (0.39–0.51)	55 (49–61)
6 months–<30 months				
Not vaccinated	1032 (90.6)	2,371 (86.5)	Ref.	Ref.
Incomplete	36 (3.2)	67 (2.4)	1.02 (0.66–1.59)	-2 (-59–34)
Complete	71 (6.2)	303 (11.1)	0.54 (0.41–0.71)	46 (29–59)
30 months–<5 years				
Not vaccinated	1,272 (93.1)	2,108 (85.7)	Ref.	Ref.
Incomplete	9 (0.6)	21 (0.9)	0.59 (0.26–1.35)	41 (-35–74)
Complete	86 (6.3)	329 (13.4)	0.38 (0.29–0.50)	62 (50–71)
5 years–<9 years				
Not vaccinated	2,917 (93.6)	5,985 (87.7)	Ref.	Ref.
Incomplete	16 (0.5)	49 (0.7)	0.69 (0.38–1.25)	31 (-25–62)
Complete	185 (5.9)	789 (11.6)	0.45 (0.37–0.53)	55 (47–63)
Vaccine doses received in 2022				
6 months–<9 years				
Not vaccinated	5,221 (92.8)	10,464 (87)	Ref.	Ref.
One dose	389 (6.9)	1,504 (12.5)	0.48 (0.42–0.54)	52 (46–58)
Two doses	14 (0.3)	54 (0.5)	0.54 (0.29–1.01)	46 (-1–71)
6 months–<30 months				
Not vaccinated	1,032 (90.6)	2,371 (86.5)	Ref.	Ref.
One dose	95 (8.3)	322 (11.7)	0.64 (0.50–0.83)	36 (17–50)
Two doses	12 (1.1)	48 (1.8)	0.56 (0.28–1.11)	44 (-11–72)
30 months–<5 years				
Not vaccinated	1,272 (93)	2,108 (85.8)	Ref.	Ref.
One dose	93 (6.8)	347 (14.1)	0.39 (0.30–0.50)	61 (50–70)
Two doses	2 (0.2)	3 (0.1)	0.78 (0.12–5.24)	22 (-424–88)
5 years–<9 years				
Not vaccinated	2,917 (93.5)	5,985 (87.7)	Ref.	Ref.
One dose	201 (6.5)	835 (12.2)	0.46 (0.39–0.55)	54 (45–61)
Two doses	0	3 (0.1)	–	–

VE: Vaccine effectiveness; Ref: Reference group; Complete: Two doses in 2022 or one dose in 2022 and at least one prior dose; Incomplete: One dose in 2022 and no prior dose; –: No observation



* Adjusted by sex

Figure 8. Adjusted VE stratified by age group, completeness, and doses received in 2022 among children

3.6. Influenza vaccine effectiveness against influenza associated hospitalisation

3.6.1. Case-control matching

Of the 41,567 influenza cases eligible for matching for estimation of VE against laboratory confirmed influenza, there were 3,541 (8.5%) cases recorded as hospitalised due to influenza and were included in the analysis for estimation of VE against hospitalisation. Cases with unknown hospitalisation status ($n=37,991$) and those recorded as not hospitalised ($n=35$) were excluded. Likewise, of the 516,702 COVID-19 negative controls, 516,690 were included for matching with the hospitalised cases. Controls who were recorded as hospitalised due to COVID-19 during the study period were excluded ($n=12$). Cases and controls were matched on postcode, specimen collection date (± 14 days), and age. Of the 3,541 cases with a hospitalisation recorded, 3,058 (86.3%) cases matched to 31,504 controls (26,847 controls matched to 2,919 unique cases and 4,657 controls matched to >1 case). The controls who matched to more than 1 case were randomly assigned to match 1 case only and maximum number of controls matched per case was restricted to 10 per case. After random selection and restriction, 3,037 cases and 19,042 controls were used to estimate VE against influenza hospitalisation. Of these, 38% of the cases ($n=1,161$) had 10 controls assigned to them and 44% had 1–5 controls per case.

3.6.2. Estimates of Influenza vaccine effectiveness against a notified case being hospitalised

Overall, VE and VE_{adj} by sex against hospitalisation due to influenza was 54% (95% CI 48–59) (Table 7). Vaccine uptake was higher among controls (28.6%) compared to cases (16.5%) ($P < 0.001$). When stratified by age group, VE_{adj} was highest for 5 years–<9 years (84%, 95% CI: 48–95). The point estimates were lower for children <5 years of age (6 months–<30 months: 44%, 95% CI -33–77; 30 months–<5 years: 41%, 95% CI: -46–76) and adults ≥65 years of age (47%, 95% CI 38–54) compared to other age groups. The overall estimates represented VE against influenza A as only a small number of influenza B cases were hospitalised (n=3).

Table 7. Estimates of vaccine effectiveness against hospitalisation by vaccination status, age groups and influenza virus types, Queensland, 2022

	Case n (%)	Control n (%)	Crude OR (95% CI)	Crude VE% (95% CI)	VE _{adj} % (95% CI)
Overall					
Not vaccinated	2,537 (83.5)	13,589 (71.4)	Ref.	Ref.	Ref.
Vaccinated	500 (16.5)	5,453 (28.6)	0.46 (0.41–0.52)	54 (48–59)	54 (48–59)
6 months–<30 months					
Not vaccinated	141 (94.6)	383 (92.7)	Ref.	Ref.	Ref.
Vaccinated	8 (5.4)	30 (7.3)	0.57 (0.24–1.34)	43 (-34–76)	44 (-33–77)
30 months–<5 years					
Not vaccinated	118 (92.9)	240 (90.6)	Ref.	Ref.	Ref.
Vaccinated	9 (7.1)	25 (9.4)	0.60 (0.24–1.47)	40 (-47–76)	41 (-46–76)
5 years–<9 years					
Not vaccinated	166 (98.2)	526 (89.6)	Ref.	Ref.	Ref.
Vaccinated	3 (1.8)	62 (10.5)	0.16 (0.05–0.52)	84 (49–95)	84 (48–95)
9 years–<20 years					
Not vaccinated	297 (96.4)	1,649 (91.5)	Ref.	Ref.	Ref.
Vaccinated	11 (3.6)	153 (8.5)	0.42 (0.22–0.79)	58 (21–78)	59 (21–78)
20 years–<65 years					
Not vaccinated	1,217 (88.7)	7,899 (77.2)	Ref.	Ref.	Ref.
Vaccinated	155 (11.3)	2,331 (22.8)	0.40 (0.33–0.48)	60 (52–67)	61 (53–68)
≥65 years					
Not vaccinated	598 (65.6)	2,892 (50.4)	Ref.	Ref.	Ref.
Vaccinated	314 (34.4)	2,852 (49.6)	0.53 (0.46–0.62)	47 (38–54)	47 (38–54)
Influenza virus types					
Influenza A					
Not vaccinated	2,528 (83.5)	13,598 (71.4)	Ref.	Ref.	Ref.
Vaccinated	500 (16.5)	5,453 (28.6)	0.47 (0.42–0.52)	53 (48–58)	54 (48–59)
Influenza B					
Not vaccinated	3 (100)	16,123 (73)	Ref.	Ref.	Ref.
Vaccinated	0	5,953 (27)	–	–	–

VE: Vaccine effectiveness; Ref.: Reference group; VE_{adj}: VE adjusted by sex; – : No observation

Assessing VE against hospitalisation by completeness for 6 months–<9 years old, a high proportion of hospitalised cases and matched controls were unvaccinated (Table 8). VE_{adj} was higher among the children (6 months–<9 years old) who were completely vaccinated (67%, 95% CI: 39–82) compared to incompletely vaccinated (17%, 95% CI: -146–72) (Table 8). The

point estimates of effectiveness of complete doses compared to incomplete dose were higher among all age groups of children, except 30 months–<5 years old. VE_{adj} of single dose recipients in 2022 showed highest effectiveness among 5 years–<9 years old (84%, 95% CI 48–95) as with the complete vaccination status (89%, 95% CI 52–97) for the age group.

Table 8. Estimates of vaccine effectiveness against hospitalisation by vaccine completeness and doses among children, Queensland, 2022

	Case n (%)	Control n (%)	Crude OR (95% CI)	Crude VE % (95% CI)	VE_{adj} % (95% CI)
Vaccine completeness					
6 months–<9 years					
Not vaccinated	425 (95.5)	1,149 (90.7)	Ref.	Ref.	Ref.
Incomplete	6 (1.4)	16 (1.3)	0.82 (0.28–2.42)	18 (-142–72)	17 (-146–72)
Complete	14 (3.1)	101 (8)	0.33 (0.18–0.61)	67 (39–82)	67 (39–82)
6 months–<30 months					
Not vaccinated	141 (94.6)	383 (92.7)	Ref.	Ref.	Ref.
Incomplete	4 (2.7)	6 (1.5)	1.30 (0.30–5.68)	-30 (-468–70)	-37 (-496–69)
Complete	4 (2.7)	24 (5.8)	0.40 (0.13–1.19)	60 (-19–87)	62 (-15–87)
30 months–<5 years					
Not vaccinated	118 (92.9)	240 (90.6)	Ref.	Ref.	Ref.
Incomplete	1 (0.8)	3 (1.1)	0.50 (0.04–5.81)	50 (-468–70)	49 (-480–96)
Complete	8 (6.3)	22 (8.3)	0.61 (0.24–1.53)	39 (-19–87)	40 (-53–76)
5 years–<9 years					
Not vaccinated	166 (98.2)	526 (89.5)	Ref.	Ref.	Ref.
Incomplete	1 (0.6)	7 (1.2)	0.60 (0.07–5)	40 (-400–93)	40 (-404–93)
Complete	2 (1.2)	55 (9.3)	0.12 (0.03–0.49)	88 (51–97)	89 (52–97)
Vaccine doses received in 2022					
6 months–<9 years					
Not vaccinated	425 (95.5)	1,149 (90.8)	Ref.	Ref.	Ref.
One dose	20 (4.5)	113 (8.9)	0.40 (0.24–0.69)	60 (31–76)	60 (31–76)
Two doses	0	4 (0.3)	–	–	–
6 months–<30 months					
Not vaccinated	141 (94.6)	383 (92.7)	Ref.	Ref.	Ref.
One dose	8 (5.4)	26 (6.3)	0.63 (0.26–1.50)	37 (-50–74)	37 (-50–74)
Two doses	0	4 (1)	–	–	–
30 months–<5 years					
Not vaccinated	118 (92.9)	240 (90.6)	Ref.	Ref.	Ref.
One dose	9 (7.1)	25 (9.4)	0.60 (0.24–1.47)	40 (-47–76)	40 (-47–76)
Two doses	–	–	–	–	–
5 years–<9 years					
Not vaccinated	3 (1.8)	62 (10.5)	Ref.	Ref.	Ref.
One dose	166 (98.2)	526 (89.5)	0.16 (0.05–0.52)	84 (48–95)	84 (48–95)
Two doses	–	–	–	–	–

VE: Vaccine effectiveness; Ref: Reference group; VE_{adj} : VE adjusted by sex; Complete: Two doses in 2022 or one dose in 2022 and at least one prior dose; Incomplete: One dose in 2022 and no prior dose; – : No observation

3.7. Sensitivity analysis

3.7.1. Matching on statistical area, age, and specimen collection

After matching on SA2, age, and specimen collection using similar criteria as for the primary analysis for VE, 27,412 cases and 86,837 controls were included in the analysis (Table 9). Overall, VE and VE_{adj} against laboratory confirmed influenza were similar to the estimates after matching on postcode (Tables 5 and 9).

Table 9. Estimates of vaccine effectiveness against laboratory confirmed influenza after matching on SA2, age, specimen collection, Queensland, 2022

	Case n (%)	Control n (%)	Crude OR (95% CI)	Crude VE % (95% CI)	VE _{adj} (95% CI)
Overall					
<i>Not vaccinated</i>	23,022 (84)	65,072 (75)	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
<i>Vaccinated</i>	4,390 (16)	21,765 (25)	0.61 (0.58–0.63)	39 (37–42)	40 (37–42)

Vaccine effectiveness; Ref: Reference group; VE_{adj}: VE adjusted by sex

3.7.2. Using COVID-19 positive and negative controls

The sensitivity analysis included positive and negative COVID-19 tests and used similar matching criteria on postcode, age, and specimen collection as for the primary analysis. This provided 37,600 cases (positive COVID-19: n=5,230, negative COVID-19: n=29,558, no COVID-19 test: n=2,812) and 246,376 controls (positive COVID-19: n=136,990, negative COVID-19: n= 109,386) for the analysis (Table 10). The overall VE_{adj} against influenza notifications was 36% (95% CI: 36–38) and after stratification by COVID-19 test results, VE_{adj} for negative COVID-19 (40%, 95% CI 37–42) was higher than for positive COVID-19 (23%, 95% CI 16–30).

Table 10. Estimates of vaccine effectiveness against laboratory confirmed influenza including positive and negative COVID-19 tests, Queensland, 2022

	Case n (%)	Control n (%)	Crude OR (95% CI)	Crude VE % (95% CI)	VE _{adj} (95% CI)
Overall					
<i>Not vaccinated</i>	32,024 (85.2)	190,565 (77.3)	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
<i>Vaccinated</i>	5,576 (14.8)	55,811 (22.7)	0.64 (0.62–0.66)	36 (34–38)	36 (36–38)
COVID-19 positive					
<i>Not vaccinated</i>	4,353 (83.2)	107,142 (78.2)	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
<i>Vaccinated</i>	877 (16.8)	29,848 (21.8)	0.79 (0.72–0.87)	21 (13–28)	23 (16–30)
COVID-19 negative					
<i>Not vaccinated</i>	25,127 (85)	83,423 (76.3)	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
<i>Vaccinated</i>	4,431 (15)	25,963 (23.7)	0.61 (0.58–0.63)	39 (37–42)	40 (37–42)

VE: Vaccine effectiveness; Ref: Reference group; VE_{adj}: VE adjusted by sex

4. Discussion

In Queensland, the influenza season started earlier in 2022 than the previous five years (2017–2021). Influenza notifications also returned to frequencies similar to the COVID-19 pre-pandemic period (2017–2019) compared with the smaller number of notifications in 2020 and 2021 due to COVID-19 related changes in social behaviours and restrictions (45, 46). Inter-seasonal activity was observed over the study period 2017–2022 except during 2020/2021. In 2022, influenza started in inter-seasonal period, which could be due to different social factors after the COVID-19 pandemic. Thus, the notification rates were higher than the high threshold in inter-seasonal period. Inter-seasonal influenza activity could be influenced by changing climatic patterns; increase in laboratory testing rates; increase in international travellers; increase in influenza vaccine coverage with higher VE within the season and; better vaccine match during the seasonal period, thus pushing and amplifying influenza activity into the inter-seasonal period (36, 46-49). The inter-seasonal activity was mostly contributed by the notifications in the tropical region as previously reported in Queensland (36). Climatic conditions can favour such an inter-seasonality pattern in tropical regions (50). The overall influenza notification rates were higher among children <9 years old and adults above 70 years old. These correspond to poorer hygiene practices and lower level of natural immunity among children and waning immunity and poor vaccine response among elderly (51, 52).

Following public funding of free influenza vaccine for Queenslanders in 2022, the overall VE of any dose of vaccine was estimated to be 39% against influenza notification. A majority of the cases included in our study were due to influenza A (99.7%), and thus VE was similar against this influenza virus type. VE was lower for children 6 months–<30 months (37%) compared to 30 months–<5 years of age (61%). This could be explained by the low level of natural immunity among the youngest birth cohort who were much less likely to have been exposed to influenza viruses in the previous years 2020–2021, when a small number of influenza cases were notified. The older cohort of children also had a greater opportunity to receive complete vaccine doses and be exposed to circulating virus in earlier years compared to younger children. As expected, VE decreased with increasing age and was lowest for those ≥65 years old, which could be attributed to waning immunity and a weaker immune response against vaccine with ageing. The effectiveness of complete doses was observed with significantly higher VE (55%) among children <9 years compared to incomplete dose recipients (18%). The higher effectiveness of two doses compared to one dose received in 2022 was observed only among those 6 months–<30 months, as most of the older children were likely to have been exposed to circulating influenza, or been vaccinated, in pre-covid years, reducing the incremental benefit of two dose receipt.

Overall, VE against influenza hospitalisation (54%) was higher comparatively to VE against laboratory confirmed influenza (39%). As expected, this demonstrates effectiveness of influenza vaccine in providing better protection against a severe disease outcome. VE against hospitalisation was highest for children of 5 years–<9 years (84%), who were most likely to have acquired natural immunity in pre-COVID years. Notification rate for this birth cohort was high in 2019. The level of protection against hospitalisation among older population also remained higher compared to the protection against infection. The effectiveness represented protection against influenza A as there were very small numbers of influenza B cases (0.1%) included in the analysis. VE among children <9 years of age with complete doses and one dose in 2022 was also observed to be higher in comparison to incomplete doses recipients. Hence, as per the Australian Immunisation Handbook, children <9 years should be encouraged to receive complete dose course of influenza vaccine recommended for their age group and with no prior vaccination history (28).

With our study we reported VE estimates against laboratory confirmed influenza and hospitalisation for all age groups in Queensland. The estimates among children were in similar range as previously reported for <2 years (33%, 95% CI: 7–52), 2 years–<3 years (48%, 95% CI: 21–65), 3 years–<4 years (69%, 95% CI: 48–81), and 4 years–<6 years (56%, 95% CI : 38–68) in Queensland (31). Complete doses were also reported to provide better protection by this study, similar to our findings. Previous Australian studies estimated VE with a range of 40–79% against hospitalisation (53–59). In 2022, influenza VE against hospitalisation was estimated to be 44% (95% CI: 22%–60%) and 37% (95% CI: -13%–66%) based on the preliminary data from sentinel hospitals (Influenza Complications Alert Network) and from sentinel GPs (Australian Sentinel Practices Research Network and Victorian Sentinel Practice Influenza Network), respectively (12). These estimates are expected to differ depending on the VE against disease outcome measured, match between vaccine compositions, circulating influenza virus, geographical locations, and study designs, period and population.

One of the strengths of this study includes vaccination history obtained from the AIR by data linkage. In Australia, the overall influenza vaccination coverage in 2022 (70%) was higher than during pandemic years, 2021 (65%) and 2020 (62%) (60). Reporting of NIP vaccines to AIR was mandatory from 1 July 2021 for vaccination providers (61). There is a possibility of under-reporting of influenza vaccination to AIR. However, the under-reporting on vaccine coverage for both cases and controls is likely to be similar due to the same source of vaccination data and the absence of outcome (influenza infection) at the time of reporting. Not having the data on individual laboratory test types for influenza cases was a limitation and prevented us from restricting analyses to PCR positive cases only. However, ~96% of influenza notifications made in 2022, and included in the descriptive analysis, were confirmed by nucleic acid testing.

Various confounding factors could also bias our estimates including access to health care facilities for laboratory testing and immunisation, and due to differences in demographics (sex, age, location) between cases and controls. Potential demographic confounders (age and location) in our study were managed through matching. Differences due to access to healthcare facilities are likely to have been minimised by the availability of publicly funded diagnostic testing and influenza vaccine for all Queenslanders. Controls were also tested for COVID-19, which would have reduced the selection bias due to differences in healthcare access and health seeking behaviour. Overall, the impact of these biases and confounders on our findings is not able to be estimated, but where present, effects are likely to be modest and result in bias towards the null, suggesting our findings if biased represent conservative estimates of VE.

Our study included individuals tested for COVID-19 as controls. Other studies have shown that including those who test positive for COVID-19 as controls can underestimate influenza VE due to the correlation of COVID-19 vaccination and influenza vaccination behaviours (34, 35). Individuals who are less likely to be vaccinated against COVID-19 are also unlikely to be vaccinated against influenza compared to the source population (35, 62). These could be addressed in the analysis by stratification or in the study design by restriction as suggested by other authors (34). Our sensitivity analysis also showed that including COVID-19 test positive reduced the overall VE, which was observed with stratification by COVID-19 test results. We addressed this issue of confounding bias by restricting our control group to include those who had negative COVID-19 tests only in our primary analysis. The majority of influenza notifications were of type A with unknown sub-types. Of the known subtypes, influenza A H3 accounted for higher number of cases compared to influenza A H1. VE against subtypes could not be assessed to determine how well the vaccine composition matched with the circulating influenza virus. Although the primary reason of hospitalisation whether due to influenza or other co-morbidities was not assessed, our overall estimates demonstrate that the funded vaccines were effective in reducing the influenza incidence and severe outcomes associated with the disease.

5. Conclusion

In Queensland, seasonal influenza activity commenced earlier in 2022 than the previous years, with a rise in cases seen in the traditional inter-seasonal period. Influenza vaccines provided varying levels of protection against influenza notification among different age groups, which was driven by dose completeness, possibly due to natural immunity developed in previous years among children, and waning and weaker immunity against vaccination among older people. However, the level of protection against hospitalisation was moderate among all age

groups, which highlighted the significance of funded influenza vaccine in reducing severe disease outcome. This study also reminded us of the value and feasibility of estimating VE against other vaccine preventable diseases using notification data with the routine integration of AIR vaccination data.

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Chapter V:

Evaluation of a surveillance system

An evaluation of surveillance for acute flaccid paralysis in Queensland

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Prologue

Acute Flaccid Paralysis (AFP) is a notifiable condition in Queensland and is also under surveillance nationally by the Australian Paediatric Surveillance Unit (APSU), the Paediatric Active Enhanced Disease Surveillance (PAEDS), and the National Enterovirus Reference Laboratory (NERL). These multiple surveillance mechanisms have overlapping purposes and often collect similar data about AFP cases. Differences in the number of AFP cases reported between the surveillance systems in Queensland and at the national level through the APSU/PAEDS/NERL were acknowledged, which led to this review of AFP surveillance in Queensland. This project was conducted to better understand the usefulness of having AFP as a notifiable condition in Queensland and to provide recommendations based on the findings of the evaluation.

My role

I reviewed the process of AFP surveillance in Queensland and the national AFP surveillance and identified key stakeholders and informants for the evaluation of Queensland AFP surveillance system. I undertook a mixed methods study design to evaluate the relevant system attributes using the Centers for Disease Control and Prevention framework. I extracted data from the Queensland Notifiable Conditions System; developed semi-structured interview questionnaires; evaluated information after discussion with the stakeholders; and analysed the data. I drafted this Chapter and prepared a final report with recommendations for dissemination to stakeholders and decision makers.

Lessons learned

I understood the significance of evaluating a surveillance system. An existing surveillance system should be evaluated to determine if it is monitoring a disease effectively and efficiently. As the system depends on the method of data collection which determines quality of the data, there are a range of factors that needs to be considered to assess its usefulness and reliability. Guidelines are helpful to focus on these factors or attributes to be evaluated. The aim is to make recommendations after evaluation for improvements or changes of the surveillance system. A lesson learned was the importance of qualitative study components and interpreting findings from stakeholder opinions and qualitative data. I also learned to develop semi-structured questionnaires, including open-ended questions for discussion with the key informants.

Public health impact

A surveillance system for a notifiable condition should be simple in terms of operation. A complex system increases the likelihood of inaccurate disease monitoring with the possibility of missing cases. Likewise, multiple surveillance systems for the same condition may create confusion and duplication of effort. This evaluation demonstrated issues with AFP surveillance in Queensland and led to the recommendation that serious consideration be given to removing AFP from the notifiable conditions list. Whether or not this occurs, efforts should be made to strengthen existing surveillance mechanisms. Removing AFP's status as a notifiable condition would require careful consideration from the Queensland Government and would involve making legislative amendments.

Acknowledgements

I thank my supervisors for providing a different public health research experience. I appreciate their support in developing this project independently and providing constructive feedback. I also acknowledge the stakeholders— the Australian Government Department of Health and Aged Care, the APSU, the NERL, the PAEDS, Queensland Public Health Units, Pathology Queensland, and the Communicable Diseases Branch for participating in this evaluation. This project would not have been complete without their engagement and feedback.

Abstract

Background: The World Health Organization (WHO) recommends surveillance for acute flaccid paralysis (AFP) in children younger than 15 years of age for certification of polio-free status. AFP is a clinically notifiable condition in Queensland. As well as the requirement of AFP notification to Queensland Health there are other national surveillance mechanisms for AFP, including the Australian Paediatric Surveillance Unit (APSU), the National Enterovirus Reference Laboratory (NERL), and the Paediatric Active Enhanced Disease Surveillance (PAEDS). There are concerns about overlapping activity and purpose of these surveillance mechanisms which may result in confusion and variations in the number of cases reported. This evaluation was aimed at understanding the usefulness of AFP surveillance and to add to discussions about whether AFP should remain a notifiable condition in Queensland.

Methods: The surveillance system attributes (simplicity, data quality, sensitivity, and timeliness) were evaluated using an exploratory mixed method study design based on qualitative and quantitative data analyses. Sources of data for AFP cases from January 2008–July 2023 were Queensland Health Notifiable Conditions System (NoCS) and the national AFP surveillance system (data held by NERL). The stakeholders consulted were the Australian Government Department of Health, the NERL, the PAEDS, Pathology Queensland, and Queensland Health Communicable Diseases Branch and Public Health Units (PHUs).

Results: During January 2008–July 2023, among children <15 years of age, there were 151 AFP cases notified to the national AFP surveillance system and 100 cases notified to NoCS. Ten cases were notified by PHUs to the national AFP surveillance system, of which only one was not notified by the APSU/PAEDS. Duplication of AFP notification was a key issue with Queensland AFP surveillance. Differences in case definitions with the national AFP surveillance system, lack of awareness of reporting AFP cases to Queensland Health among those involved in the notifications, and unclear instructions on notification procedures were identified. Major issues were with delayed timeliness of notification and poor sensitivity of Queensland AFP surveillance.

Conclusion: Redundancy, delayed notification, and lower sensitivity demonstrated poor functionality of Queensland state-based AFP surveillance. These findings indicate no additional benefits of AFP being a notifiable condition in Queensland. As national AFP surveillance has met the WHO targets in recent years at the jurisdictional level, there is a minimal risk if AFP does not remain a notifiable condition in Queensland. An alternative option would be improving Queensland AFP surveillance by streamlining with the national AFP surveillance system to avoid confusion and duplication.

1. Background

Acute flaccid paralysis (AFP) is a clinical syndrome caused by infectious or non-infectious agents (1). It is defined by the World Health Organization (WHO) as a syndrome “characterised by rapid onset of weakness of an individual’s extremities, often including weakness of the muscles of respiration and swallowing, progressing to maximum severity within 1–10 days” (2). Part of the purpose of AFP surveillance is to identify and monitor AFP cases related to poliomyelitis, enterovirus 71, and botulism to take immediate public health action, and meet the WHO AFP surveillance performance indicator target for polio-free countries (1). AFP surveillance has been useful to monitor the incidence of polio as we approach global eradication and to allow appropriate public health actions to prevent and control transmission of the disease (2, 3).

Polio is an infectious disease caused by a picornavirus and transmitted by faecal oral route (4). Approximately one in 200 infections cause irreversible paralysis (usually of the legs), of which 5–10% die due to immobilisation of breathing muscles (5). The disease is now considered eliminated in most countries after the introduction of a polio vaccine in 1950s (4, 6). However, pockets of polio still persist in Pakistan and Afghanistan (7), which poses an ongoing risk of importation of cases to polio free countries. Although vaccination coverage for polio among children at the five years of age timepoint is approximately 95% in Australia (8), uptake is lower in certain regions (9). High quality polio surveillance is needed to allow for the rapid detection and response to imported disease in polio-free countries.

AFP surveillance is considered a gold standard public health process for the detection of poliomyelitis cases (10). The WHO targets for AFP surveillance require at least one case of non-polio AFP to be detected per 100,000 population per year in those younger than 15 years of age (10). The requirement is 2 per 100,000 per year in polio-endemic countries (10). In 2021, there were 84,684 AFP cases reported globally, with a non-poliomyelitis AFP rate of 4.39 per 100,000 population per year in those younger than 15 years of age, five wild poliovirus type 1 cases, and 597 circulating vaccine-derived poliovirus cases identified (11). In Australia, there were 63 AFP cases reported in 2021 (non-polio incidence rate of 1.31 per 100,000 population per year in those younger than 15 years of age) of which 62% had an adequate stool specimens collected (11, 12). Previously, there were 111 confirmed cases of AFP in the country from March 1995 to December 1998, with an incidence rate of 0.71 per 100,000 population per year in those younger than 15 years of age (13). None of these cases were diagnosed with polio (13). Approximately 96% of the reported AFP cases among children were hospitalised and 33% required intensive care (14).

In Australia and all jurisdictions other than Queensland, AFP is not a notifiable condition. However, AFP surveillance is a requirement to document maintenance of Australia's polio-free status and detect imported cases and vaccine associated paralytic polio (15). The national AFP surveillance system includes the Australian Paediatric Surveillance Unit (APSU), the National Enterovirus Reference Laboratory (NERL), and the Paediatric Active Enhanced Disease Surveillance (PAEDS) (16). In Queensland, AFP notification is required under the Public Health Act 2005 and the subordinate Public Health Regulation 2018 (17, 18) .

Public health surveillance is a cycle of information between healthcare providers, public health agencies, and the public (19), that involves “the ongoing, systematic collection, analysis, and interpretation of health-related data essential to planning, implementation, and evaluation of public health practice” (20). Therefore, an existing surveillance system should be evaluated to determine if it is monitoring a disease effectively and efficiently. Such an evaluation is useful to make recommendations for improvements or changes of the surveillance system. The requirement of AFP notification to both Queensland Health and other systems by diagnosing clinicians has shown overlapping functionality and differences in the number of cases reported. As AFP surveillance is nationally co-ordinated by the APSU, the PAEDS, and the NERL, this evaluation reviewed AFP surveillance to consider if AFP should remain a notifiable condition in Queensland as per Schedule 1 in the Public Health Regulation 2018.

2. Methods

A review of the AFP notification procedure in Queensland was conducted by reviewing Queensland Health AFP Guidelines for Public Health Units (PHUs) and the APSU AFP study protocol (1, 15, 21). The Queensland AFP surveillance system was evaluated using an exploratory mixed method study design based on qualitative and quantitative data analyses.

2.1. Evaluation of the surveillance system attributes

The following surveillance system attributes were assessed using the Centers for Disease Control and Prevention Guidelines for evaluating public health surveillance systems (22).

2.1.1. Simplicity

Simplicity refers to the flow of information or data, structure of reporting, and ease of operation (22). This was determined based on the review of AFP notification process in Queensland and discussion with all the stakeholders. The relevant key informants were asked if it was simple or complex to report AFP cases and any duplication or inefficiencies could be identified.

2.1.2. Data quality

Data quality was determined by the completeness of the data required for reporting purposes (determining the level of missing data) and any duplication of cases notified. Variables assessed were age, sex, date of birth, date of diagnosis, onset date, specimen collection date, assigned PHU, and Hospital and Health Service.

2.1.3. Sensitivity

Sensitivity refers to the proportion of cases with a disease detected by the system (22). The number of cases reported by the national AFP surveillance system for Queensland was considered as the denominator for the calculation. This was calculated as number of cases notified to Queensland Health Notifiable Conditions System (NoCS) divided by number of cases reported to the national AFP surveillance system.

Sensitivity was also determined as the ability of the surveillance system to meet the WHO requirements for AFP surveillance by calculation of notification rates (at least one case of non-polio AFP per 100,000 population per year in those younger than 15 years of age). The attribute was also assessed by matching Queensland AFP cases with the national AFP surveillance cases.

2.1.4. Timeliness

Timeliness refers to the duration taken or time interval between steps of notification process (22). It was calculated as difference in dates between provisional diagnosis by clinician and notification; specimen collection and diagnosis; and data entry into the system from notification date. Timeliness of notification from onset date was compared against the WHO recommendations. The system attribute was also evaluated based on discussion with stakeholders.

2.2. Usefulness of the surveillance system

The stakeholders were asked to comment on the usefulness and advantages of requiring AFP notification in Queensland and to identify any gaps in surveillance. Feedback was also sought on possible risks and impact if Queensland AFP notification ceased or if AFP should remain a notifiable condition in Queensland.

2.3. Source of data

National AFP surveillance data on Queensland cases from January 2008 to July 2023 were provided by the NERL on 17 July 2023. Queensland AFP surveillance data from NoCS for the same duration were extracted on 19 July 2023. Notification rate was calculated using mid-

year population estimate of Queensland obtained from the Australian Bureau of Statistics (23). Data fields included variables to allow matching of cases and to determine timeliness of notification and laboratory diagnosis. Qualitative data were collected through semi-structured interviews (Appendix).

2.4. Data analysis

Counts, proportions, means, and confidence intervals were calculated using Microsoft Excel Version 2202 (Microsoft, Redmond, Washington) and Stata version SE 16.1 (StataCorp, College Station, TX). Notification rates were estimated for Queensland cases of all ages and for children younger than 15 years old. Individual AFP cases reported to the national AFP surveillance system and Queensland Health were matched by unique identifiers generated using first two initials of the first name and last name, first initial of sex, and date of birth.

2.5. Stakeholders

Stakeholders were identified based on the AFP notification procedure (Table 1). One-to-one semi-structured interviews were conducted with key informants of stakeholders to evaluate the system attributes, determine usefulness of NoCS AFP surveillance, and understand instances when NoCS data were used to inform public health action.

Table 1. Key stakeholders and their roles in Queensland AFP surveillance

Stakeholders	Roles in AFP surveillance
Australian Government Department of Health and Aged Care	Number of key informants: 1 Co-ordinates with the APSU/PAEDS/NERL and the Polio Expert Panel to obtain reports on AFP cases from all states/territories of Australia
Communicable Diseases Branch (CDB), Queensland Health	Number of key informants: 2 - Receives AFP notifications from across Queensland, including the PAEDS nurses at the Queensland Children's Hospital, clinicians at Queensland hospitals, and PHUs - Notifies PHUs of AFP cases for follow up - Monitors laboratory-based polio notifications

Stakeholders	Roles in AFP surveillance
National Enterovirus Reference Laboratory (NERL), Victorian Infectious Diseases Reference Laboratory (VIDRL)	Number of key informants: 2 ▪ Virological testing of stool specimens from AFP cases and reporting to Pathology Queensland Central laboratory, Royal Brisbane Women's Hospital ▪ Co-ordinates with clinicians/PHUs to ensure case details are collected as per the AFP APSU form
Paediatric Active Enhanced Disease Surveillance (PAEDS)	Number of key informants: 2 ▪ Identifies AFP cases at the Queensland Children's Hospital based on the APSU AFP case definition ▪ Notifies the CDB, Queensland Health
Pathology Queensland Central laboratory, Royal Brisbane Women's Hospital	Number of key informants: 1 ▪ Processes stool samples received from hospital diagnosing AFP cases to send to the NERL, VIDRL ▪ Ensures samples sent for testing meet the clinical criteria ▪ Enters results in the laboratory database, informs referring clinicians/hospitals if positive
Public Health Units (PHUs), Queensland	Number of key informants: 2* ▪ May receive notifications directly from treating clinicians ▪ Liaises with clinicians to collect case information and request stool specimens ▪ Works with the CDB to ensure complete data collection

* Key informants from two different Queensland public health units

Following the review of the surveillance system and the outcomes measured after evaluation of the system attributes, recommendations relating to improving AFP surveillance in Queensland focusing on efficiency and harmonising existing processes were synthesized.

2.6. Ethics

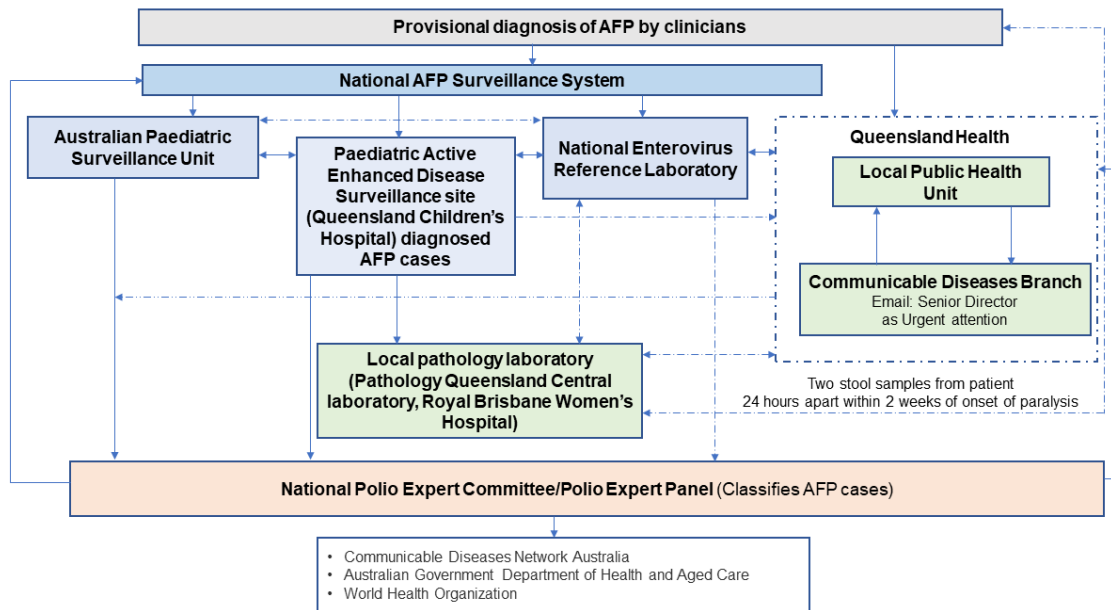
This study was conducted under the ethics approval from the Australian National University (which includes waiver of consent for use of data in research for Master of Philosophy in Applied Epidemiology students for 'Outbreak Investigation' and 'Surveillance in Public Health' projects Protocol: 2017/909).

3. Results

3.1. National and Queensland AFP surveillance systems

National AFP surveillance was commenced in 1995 by the APSU as a part of Australia's commitment to the WHO program for the global eradication of poliomyelitis (24). The APSU is responsible for sending monthly report cards to paediatricians and child health specialists to obtain information on newly diagnosed AFP patients (24). The PAEDS network was initiated in 2007 to conduct active, hospital-based surveillance of serious childhood conditions, including AFP, other vaccine preventable diseases, and adverse events following immunisation (25). The APSU collaborates with the PAEDS for active AFP case ascertainment by surveillance nurses based in seven participating hospitals around Australia (26, 27). The national AFP surveillance program has been co-ordinated at the NERL, Victorian Infectious Diseases Reference Laboratory (VIDRL) since 2000 in collaboration with the APSU (28). The National AFP surveillance Coordinator at the NERL tasks the Polio Expert Panel (PEP) to review and classify AFP cases (non-polio AFP, AFP with more information required, polio compatible AFP, poliomyelitis, and non-AFP) (29). The PEP is a subcommittee of the Communicable Diseases Network Australia (CDNA) and reports to the Australian Government Department of Health and Aged Care, the CDNA, and the WHO (29).

AFP was made notifiable in Queensland on 8 June 2001 (30), and requires immediate notification irrespective of the cause identified (1, 21). Notification is based on provisional or clinical diagnosis of all individuals by clinicians (21). Clinicians are required to notify AFP cases to local PHUs, which then reports to the CDB, Queensland Health. Diagnosing clinicians may also report AFP cases to the APSU, and there is an active in-hospital surveillance for cases by the PAEDS nurses at the Queensland Children's Hospital. In order to meet surveillance standards, clinicians are required to request stool specimens to be sent to a local pathology laboratory (Pathology Queensland Central laboratory at Royal Brisbane Women's Hospital), which organises the samples to be sent to the NERL, VIDRL. The National Polio Expert Committee (Polio Expert Panel) then reviews clinical and laboratory data to classify AFP cases (Figure 1). The local pathology laboratory receives laboratory test results from the NERL and provides a report to the referring clinicians, PHUs and the CDB.



AFP: Acute flaccid paralysis

Figure 1. AFP notification procedure based on Queensland Health guidelines for public health units and the Australian Paediatric Surveillance Unit AFP study protocol (1, 15, 21, 29)

3.2. Simplicity

The stakeholders reported that the AFP notification process was simple in terms of notifying to their respective surveillance systems. However, there was complexity identified due to redundancy in notifying cases to both Queensland AFP and the national AFP surveillance systems. Duplication of reporting cases was identified as a key issue due to the following reasons:

- Differences/similarities in case definitions between surveillance systems (Table 2).
- Lack of awareness among clinicians and PHUs of all notification pathways.
- Lack of clear instructions for PHUs and clinicians.
- Confusion between separate suspected polio and AFP notification requirements.

Table 2. APSU and Queensland Health case definitions

AFP surveillance	Case definitions
APSU/PAEDS/NERL	“Please report any child less than 15 years of age with acute flaccid paralysis in one or more limbs or acute onset of bulbar paralysis” (15)
Queensland Health	“A person of any age with acute flaccid paralysis [1] [2] [1] WHO defines AFP syndrome as ‘characterised by rapid onset of weakness of an individual's extremities, often including weakness of the muscles of respiration and swallowing, progressing to maximum severity within 1-10 days. The term ‘flaccid’ indicates the absence of spasticity or other signs of disordered central nervous system (CNS) motor tracts such as hyperflexia, clonus, or extensor plantar responses’ (World Health Organization 1993 WHO/MNH/EPI/93.3. Geneva). [2] APSU defines AFP as the acute onset of flaccid paralysis in one or more limb/s or acute onset of bulbar palsy.”

Lack of awareness, inadequate instructions, and confusion were identified as issues based on the following responses from the key informants.

Redundancy

“it was basically a total duplication and we thought....that two forms have been filled up the same information” — PHU registrar (on submission of AFP APSU form and NoCS case report form)

“...duplicate the work at this end when we have a notification coming from PAEDS or when it comes in from a public health unit or from a GP or clinician.” — NERL staff (on receiving multiple AFP APSU forms for a same case submitted by clinicians and PHUs).

Lack of awareness

“...was not aware that it was notifiable, but when she spoke with the ID [Infectious diseases] team specifically the microbiology registrar, she was the one who was aware that AFP cases had to be contacted or notified to public health” — PHU registrar (on lack of awareness of AFP as a notifiable condition among clinician).

“...for most public health units, it's relatively rare.... public health units, maybe from their size and their location.....means that they've just got more practice of doing it” — CDB staff (on notification of AFP cases by PHU).

Confusion and need for instructions

“Sometimes there is a bit of confusion with AFP and polio.... One is based on the laboratory results for polio ... another one is clinical notification for AFP....change the polio notification to AFP or .. or vice-versa.. there is no SOP or clear instruction how we manage the AFP and polio” — CDB staff (on confusion among PHU staff on recording a case as a suspected polio or AFP in NoCS).

3.3. Data quality

During January 2008–July 2023, there were 109 AFP confirmed cases of all ages from Queensland in NoCS. Other eight notifications, including ‘Not A Case’ based on case definition and/or interstate residence (n=7) and ‘Unsure’ (n=1) were excluded. Demographic details were well recorded in NoCS (Table 3). However, as AFP is a clinically notifiable condition, dates of onset of clinical presentation and diagnosis were missing for 39% and 14% of the notified cases, respectively.

Table 3. Data fields and percent of data completeness in NoCS, January 2008–July 2023

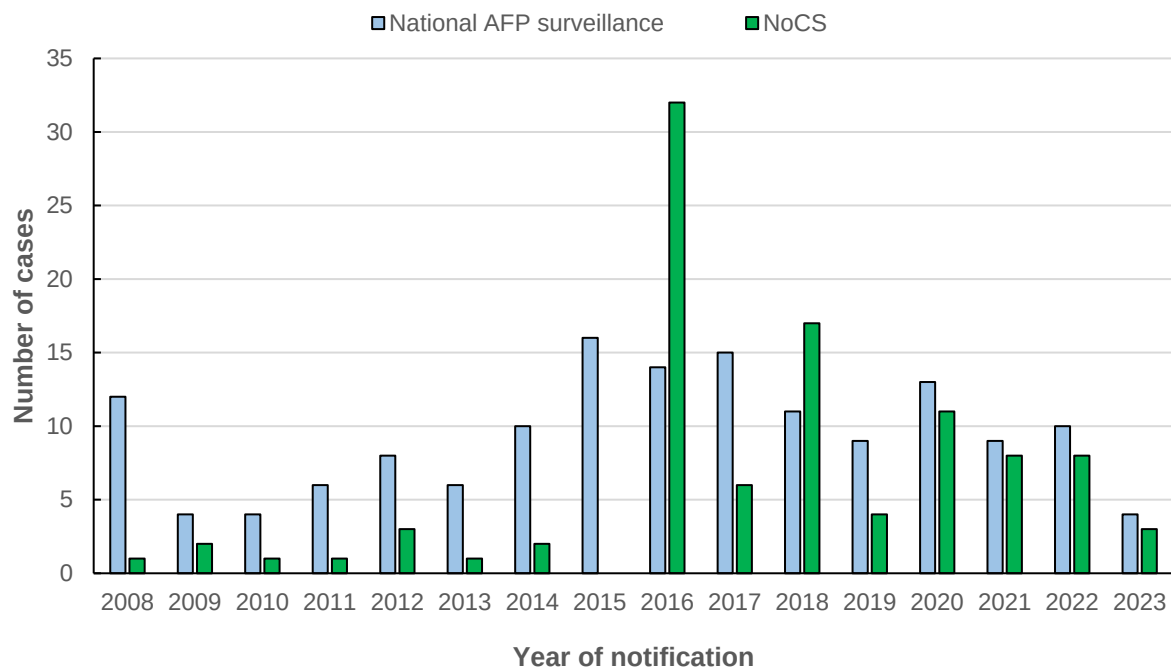
Data fields/variables	Data completeness % (n)
Sex	100% (109)
Age	100% (109)
Date of birth	100% (109)
Date of diagnosis	86% (94)
Onset date	61% (66)
Specimen collection date	87% (95)
Assigned PHU	100% (109)
Hospital and Health Services	100% (109)

3.4. Sensitivity

A total of 151 AFP cases from Queensland were notified to the national AFP surveillance system during the period (January 2008–July 2023), including confirmed (n=141), case with pending stool specimen (n=1), polio compatible (poliomyelitis could not be excluded based on the available clinical and laboratory information) (n=1), and polio compatible-zero evidence (cases without clinical questionnaire) (n=8). Polio compatible-zero evidence (reported to the WHO since 2010), and polio compatible were included in the analysis. Duplicates (n=72) and error or non-AFP cases (n=14) were excluded.

Of the AFP confirmed cases in NoCS (n=109), 100 were <15 years of age and included in the analysis to determine sensitivity. Three of these cases were categorised as polio compatible-

zero evidence (n=2) and polio compatible (n=1) by the national AFP surveillance. After matching these cases using a unique identifier, there were 99 cases notified to both the national AFP surveillance and NoCS, 52 cases to the national AFP surveillance only, and one case to NoCS only. The one case in NoCS only was recorded as retrospectively notified by the PAEDS but did not match with any case in the dataset of the national AFP surveillance system. One of the cases with same identifier was notified twice in two different years to the national AFP surveillance but only once in NoCS and was considered to have matched only once. The number of cases notified varied by each year between the national AFP surveillance and Queensland AFP surveillance (Figure 2).



* NoCS: Notifiable Conditions System

Figure 2. Comparison of the national AFP surveillance notified cases and NoCS by year of notification date, January 2008–July 2023

A higher number of AFP cases was notified to the national AFP surveillance system compared to Queensland AFP surveillance each year (Table 4). The overall sensitivity of Queensland NoCS AFP surveillance was 66%, with a range of 0–94%. Sensitivity of Queensland AFP surveillance improved since 2014.

Table 4. Sensitivity of Queensland NoCS AFP surveillance, January 2008–July 2023*

Year**	Sensitivity (QLD notified cases/APSU cases)
2008	8% (1/12)
2009	50% (2/4)
2010	50% (2/4)
2011	– (0/6)
2012	38% (3/8)
2013	33% (2/6)
2014	70% (7/10)
2015	94% (15/16)
2016	79% (11/14)
2017	87% (13/15)
2018	91% (10/11)
2019	67% (6/9)
2020	77% (10/13)
2021	78% (7/9)
2022	80% (8/10)
2023	75% (3/4)
Overall	66% (100/151)

*Children <15 years old included in the analysis; **Year of episode date (earliest of specimen collection date, onset date, and notification date) for Queensland AFP surveillance cases; –: No observation; QLD: Queensland; APSU: Australian Paediatric Surveillance Unit

In the national AFP surveillance system, there were ten AFP cases notified by Queensland PHUs. Of these ten cases, eight were also notified by the PAEDS, one by the APSU, and only one was not notified by the APSU/PAEDS.

AFP notification rate was ≥ 1 per 100,000 population per year in those younger than 15 years of age, only in 2016, 2018, and 2020 for Queensland AFP surveillance system compared to the requirement achieved by the national AFP surveillance in most of the years from 2014 onwards for Queensland (Table 5). These lower notification rates reported by Queensland AFP surveillance do not meet the WHO requirements for sensitivity of AFP surveillance.

Table 5. AFP notification rates per 100,00 per year in Queensland by Queensland AFP surveillance and the national AFP surveillance systems, Queensland, 2008–2022

Year	NoCS notifications						APSU/NERL/PAEDS		
	All cases*			Children <15 years			Children <15 years		
	Rate	95% CI		Rate	95% CI		Rate	95% CI	
2008	0.05	0.01	0.19	0.12	0.02	0.83	0.94	0.47	1.88
2009	0.07	0.02	0.22	0.23	0.06	0.92	0.46	0.17	1.22
2010	0.02	0.00	0.16	0.11	0.02	0.80	0.45	0.17	1.21
2011	0.02	0.00	0.16	0.11	0.02	0.80	0.67	0.30	1.50
2012	0.07	0.02	0.20	0.33	0.11	1.02	0.88	0.44	1.76
2013	0.04	0.01	0.17	0.11	0.02	0.77	0.65	0.29	1.45
2014	0.09	0.03	0.23	0.21	0.05	0.86	1.07	0.58	1.99
2015	–	–	–	–	–	–	1.69	1.04	2.77
2016	0.68	0.48	0.96	3.35	2.37	4.74	1.47	0.87	2.48
2017	0.12	0.06	0.27	0.62	0.28	1.38	1.55	0.94	2.58
2018	0.36	0.23	0.57	1.74	1.08	2.80	1.13	0.62	2.03
2019	0.08	0.03	0.21	0.41	0.15	1.08	0.91	0.47	1.75
2020	0.23	0.13	0.41	1.11	0.61	2.00	1.31	0.76	2.26
2021	0.15	0.08	0.31	0.81	0.40	1.62	0.91	0.47	1.75
2022	0.17	0.09	0.33	0.81	0.41	1.62	1.01	0.54	1.88
Total	0.16	0.13	0.19	0.74	0.61	0.91	1.09	0.93	1.29

Rates indicated in bold met the WHO requirements of reporting AFP cases of ≥ 1 per 100,000 population per year for children <15 years of age

* Rate for all ages; –: No cases

3.5. Timeliness

The average duration from onset date to notification date ranged from 2–169 days, which indicated delays in notification from the day of clinical presentation (Table 6). According to the WHO AFP surveillance performance indicator for timeliness of notification, cases should be reported to public health authorities within 7 days of onset of paralysis (31). Average timeliness of recording data in NoCS (created date) from the notification date was 0–7 days in most of the years except in 2016 (34 days). Two stool specimens should be collected within 14 days (maximum 60 days) of paralysis onset and 24 hours between specimen collections as per the WHO requirements (31). Stool specimens were collected within 2 weeks of diagnosis except in 2018. Most of the cases were notified after first sample collection and these cases were likely to have been identified by Queensland Health after stool testing was requested. There were no cases notified in 2015 as per the notification date in NoCS. On further investigation, it was determined that there were 17 cases diagnosed in 2015, who were retrospectively notified to Queensland Health in 2016 by the PAEDS. For most of these retrospective notifications, onset and diagnosis dates were defaulted to hospital admission date in NoCS.

Table 6. Timeliness for NoCS AFP notified cases of all ages by year, Queensland, January 2008–July 2023

Year	Total number of cases	Average duration (days)*			
		Notification date-Onset date	Created date-notification date	Diagnosis date-sample collection date	Notification date-sample collection date
2008	1	–	0	5	39
2009	2	–	3	4	7
2010	1	–	3	0	0
2011	1	–	2	0	18
2012	3	–	1	5	12
2013	1	2	0	3	15
2014	2	44	7	14	44
2015	–	–	–	–	–
2016	32	25	34	6	255
2017	6	28	4	11	28
2018	17	169	2	187	196
2019	4	12	5	8	12
2020	11	45	2	14	39
2021	8	17	1	7	12
2022	8	8	1	–	9
2023	3	2	3	–	0
All cases	109	51	12	43	137

–: Cases with unavailable dates or those without any cases in a specific year were not included in calculation of average duration

Timeliness of AFP cases notified to the national AFP surveillance were more efficient compared to Queensland Health notification (Table 7). The average number of days of notification from onset date was 13 and, since 2015, the first stool specimen was usually collected after notification to the national AFP surveillance. A majority of the cases were first notified to the national AFP surveillance system by the APSU/PAEDS than by the PHUs (Table 7).

Table 7. Timeliness for the national AFP surveillance notified cases by year, Queensland, 2008–July 2023

Year	Total number of cases	Queensland cases average duration (days)		
		Notification date-Onset date	Notification date-first sample collection date	APSU/PAEDS/NERL notification date- PHU notification date*
2008	12	21	1	–
2009	4	9	3	–
2010	4	15	4	–
2011	6	35	8	–
2012	8	7	4	–
2013	6	13	1	–
2014	10	7	0	–
2015	16	18	-1	–
2016	14	6	0	-3
2017	15	18	-1	-6
2018	11	17	0	-7
2019	9	10	-1	-6
2020	13	7	-1	–
2021	9	6	1	-5
2022	10	16	-2	–
2023	4	3	-1	–
All cases	151	13	0	-5

–: Cases with unavailable dates or with no cases notified to the national AFP surveillance system by Queensland Health PHU were not included in calculation of average duration

* Calculated only for those cases notified to the national AFP surveillance system (as recorded) by both Queensland PHU and the APSU/PAEDS

Notification timeliness

Interviews with stakeholders determined that the timeliness of reporting of AFP cases can vary especially with the cases diagnosed at regional hospitals not covered by the PAEDS network sites. These cases may be identified when they are transferred to the Queensland Children's Hospital and can be notified to the national AFP surveillance system and Queensland Health, 7–8 days after onset. Time is usually taken to confirm that the diagnosis meets the case definition. Likewise, timely entry of information in NoCS may not occur due to lack of awareness among PHUs or confusion with polio notification as referred in the simplicity attribute. Notification from the Queensland Children's Hospital to the CDB is usually within 24 hours after identification of an AFP case.

“by the time we get a notification into NoCS.... and it gets counted by Queensland and that's not timely because it's really dependent on how long the public health unit needs to collect the information” — CDB staff (on delay in entering data into NoCS by PHU)

Laboratory testing and reporting timeliness

As per the discussions with the key informants, time from specimen collection to sending samples to the NERL from Pathology Queensland laboratory was reported to be ~5–7 days. Other reasons for a delay in testing included when a patient is not able to produce sample due to their clinical condition. Virus culture can take 14 days from sample receipt for the negative result. The usual process of requesting testing involves sending two consecutive samples to the NERL. However, if a second sample is not received from a case, the first sample is sent by the local pathology to the NERL. There can be a delay in sending negative results due to the process in place, but positive results for any pathogen are notified immediately.

3.6. Usefulness

Stakeholders suggested that Queensland AFP surveillance assists with identifying cases from regional hospitals which may not be captured by the PAEDS. It would keep clinicians informed to notify AFP cases and improve sensitivity by identifying cases from regional hospitals of Queensland. The key informant also stated that in Queensland, the PAEDS are set up only in the Queensland Children's Hospital and for Queensland wide capture of AFP cases, this would depend on coverage of the APSU.

"It is for the regional hospitals.... because there's a chance.....they may not be notified otherwise " — PAEDS nurse (on the usefulness of Queensland AFP surveillance to identify cases from hospitals other than Queensland Children's Hospital).

Data analysis showed that out of 151 cases notified to the national AFP surveillance system, ten cases were notified by PHU. Of these ten cases, only one was not identified by the APSU/PAEDS. There were 52 additional cases notified to the national AFP surveillance system, which were not notified to Queensland AFP surveillance system.

Concern was also raised that if AFP is not notifiable in Queensland, overseas trained doctors in regional hospitals of Queensland may not be aware of the requirements to notify AFP cases to the national AFP surveillance system. The issue was related to awareness of reporting AFP cases to the national AFP surveillance.

"There's a chance they may not be notified otherwise and perhaps in those hospitals you may get a lot of locum doctors participating perhaps overseas doctors who have come to work and you know they would tend to perhaps be practicing. In those hospitals cases would have been notified by appeal." — NERL staff (on

usefulness of AFP as a notifiable condition to keep overseas trained doctors informed of the requirements to report cases).

A few key informants described that it would have minimal impact on the national AFP surveillance if AFP does not remain a notifiable condition in Queensland. In addition, polio surveillance remaining in place would minimise the risk.

“I think in this current landscape of having established surveillance through other means that meets our national requirements, then having an additional level, all surveillance at a jurisdictional level isn't adding anything to it.” — CDB staff (on the usefulness of Queensland AFP surveillance over the national AFP surveillance).

“...if there's already systems in place that can easily pick that up then.. there's not too much of a value add in terms of from our perspective” — PHU public health physician (on the usefulness of Queensland AFP surveillance)

In terms of taking public health actions against AFP notifications, a recent AFP case notified in May 2023 to one of the PHUs triggered public health action, as one of the differential diagnoses was infant botulism. Resources in terms of time taken by PHU staff were required in collecting data on clinical details and immunisation status and contacting the Central pathology laboratory and pharmacy to facilitate botulism testing, and co-ordinating with clinicians and the Queensland Children's Hospital. However, it was determined botulism testing was not required for this case.

4. Discussion

The primary purpose of AFP surveillance is to detect early cases of polio in the community (3). AFP is a clinical condition due to different causative agents. Although non-specific, AFP surveillance increases the likelihood of detecting true polio cases should they occur. AFP surveillance is required to meet the WHO surveillance requirements for the maintenance of Australia's polio-free status. This requirement is being met by the national AFP surveillance mechanisms, which report to the WHO. As AFP is not a nationally notifiable disease, there is no requirement for Queensland Health to report cases to the Australian Government Department of Health and Aged Care or the WHO directly. Hence, the usefulness of AFP being a notifiable condition is questionable.

This evaluation demonstrated that with the two surveillance pathways in operation, there was confusion among stakeholders involved in the notification process. Firstly, this confusion was due to differences in case definitions and age requirements of reporting cases. The WHO requires only AFP cases of <15 years of age to be reported (3). Requirements for

clinicians/PHUs to report cases to separate surveillance systems resulted in duplication and redundancy. This was demonstrated by clinicians/PHUs submitting multiple AFP APSU forms for a same case and PHUs collecting and entering data for the case into NoCS. Lack of awareness among clinicians can lead to differences in notifications between surveillance systems. A previous Queensland study in 2007 reported that 52% clinicians were not aware of AFP as a clinical condition and 35% were not aware that AFP was a notifiable condition in Queensland (32). Hence, there was a need for awareness among clinicians and PHUs with clear instructions on the process of notification to Queensland Health and the national AFP surveillance system.

Complexity of the AFP notification process due to duplication can impact data quality, representativeness, sensitivity, and timeliness. The overall sensitivity of 66% for Queensland AFP surveillance was poor compared to the national AFP surveillance. Of significance were the AFP cases in 2015, which were only notified to NoCS in 2016. Such delays may impact on case follow up and sample testing, which impacts on our ability to understand if AFP cases may be due to polio and to meet the WHO surveillance targets. Diagnosis and onset dates were defaulted to hospital admission date for delayed notified cases in NoCS, which raises questions about data accuracy. As per the WHO surveillance indicator on completeness of case investigation for AFP, all cases should have information on full clinical and virological investigation (33). However, data on diagnosis and onset dates were incomplete, which are important for a clinically notifiable condition. Identification of AFP cases after requesting stool specimens for polio testing indicates the system in place does not meet the WHO threshold for AFP surveillance.

Some stakeholders reported being supportive of Queensland AFP surveillance for a number of reasons. Firstly, it may support the national AFP surveillance system to capture cases from regional hospitals of Queensland which are not covered by the PAEDS (Queensland Children's Hospital cases only). However, the stakeholders also indicated that such cases are identified when they are transferred to the Queensland Children's Hospital. There may be cases who are treated at the larger regional hospitals and not identified by the PAEDS. Secondly, it keeps clinicians informed to continue reporting as a notifiable condition and would increase sensitivity of detecting cases by the national AFP surveillance system. However, in every year of comparison and overall, there were more cases identified by the national AFP surveillance mechanisms compared to Queensland AFP surveillance system. The later contributed to notification of only one additional case to the national AFP surveillance, which was not identified by the APSU/PAEDS, during the study period. This case was reported by a PHU to the national AFP surveillance system. Timeliness and sensitivity of Queensland Health

AFP surveillance were not acceptable, given that immediate public health actions need to be taken against the risk of polio, particularly ensuring stool specimen collection. As more cases were reported by the national AFP surveillance systems than Queensland AFP surveillance system, this would indicate breaches of the requirements under the Public Health Act 2005 and Public Health Regulation 2018 for not reporting a notifiable condition (17, 18).

In most years, Queensland AFP surveillance has not been able to achieve a notification rate of 1 per 100,000 population per year in children younger than 15 years of age. However, the target has been achieved in recent years for Queensland by the national AFP surveillance system. This could be due to various reasons including poor acceptance of Queensland AFP surveillance system, competing priorities, and poor staffing and infrastructure to support the surveillance. Time as a resource of staff for one of the recent cases was required for follow up of case details from clinicians and to identify risks from other causative agents. As it is evident that the WHO requirement is being met by the national AFP surveillance system and other Australian jurisdictions manage risks without jurisdictional AFP surveillance, it would appear removing AFP from the list of notifiable conditions would have minimal impact on the national AFP surveillance system.

The other purpose of Queensland AFP surveillance is to monitor AFP causes other than polio, such as arbovirus infections and botulism. However, these communicable causes of AFP are separate notifiable conditions in Queensland. These together with current, routine surveillance activities, such as environmental and enterovirus surveillance in Australia, would adequately capture the epidemiology of these conditions (34). Confusion between polio and AFP surveillance has been identified from this evaluation. Furthermore, as AFP notification is created manually in NoCS, duplication and confusion has led to Queensland's surveillance system missing AFP cases and importantly polio suspected cases.

5. Recommendations

This review has identified both advantages and issues around the surveillance of AFP in Queensland, based on which the following recommendations are made:

Removing AFP as a notifiable condition in Queensland

Duplication of surveillance for AFP can be avoided by removing AFP as a notifiable condition in Queensland. This would make AFP surveillance simpler with AFP cases monitored by the national AFP surveillance process. It would also have minimal impact on polio surveillance as testing of stool specimens and collection of clinical information of suspected cases would continue. Hence, there would be minimal impact if Queensland AFP surveillance is

discontinued. This recommendation of removing AFP as a notifiable condition would require legislative amendments.

Improving AFP notification process in Queensland

While removing AFP from the list of notifiable conditions can take time, there is a need for improving and streamlining the notification process with the national AFP surveillance mechanisms. These would improve the AFP surveillance sensitivity and strengthen the national AFP surveillance system to meet the WHO requirements. The following recommendations should be considered if AFP remains a notifiable condition for the time period:

- 1) Queensland AFP surveillance should be improved by providing clear instructions to those involved in the notification process; assigning primary contact to mediate the process; and providing clarification on confirming case for follow ups.
- 2) Whilst AFP remains notifiable, to avoid delay in case notification, clinical cases of AFP should have key details including name, date of birth, home address (to allow PHU assignment) entered into NoCS as soon as possible, prior to full completion of the case report form.
- 3) Queensland AFP surveillance could be simplified by collecting same clinical information in NoCS as entered into the APSU AFP form for the national AFP surveillance system.

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7. Appendix

Semi-structured interview guide

Thanks for making time to join today's meeting.

I am Ashish Shrestha, second year MAE scholar at the Australian National University. I am based at the Communicable Diseases Branch, Queensland Health.

I am conducting this project to evaluate the surveillance of Acute Flaccid Paralysis (AFP) in Queensland.

The requirement of AFP notification to both Queensland Health and the Australian Paediatric Surveillance Unit (APSU) by diagnosing clinicians have shown overlapping purpose of AFP surveillance and differences in the number of cases reported. As AFP surveillance is nationally co-ordinated by APSU and National Enteric Reference Laboratory (NERL), this evaluation will focus to determine if AFP should remain a notifiable condition in Queensland as per Schedule 1 in the Public Health Regulation 2018.

Consent for recording

Please note that today's meeting will be recorded for the evaluation purpose of the research and will not be shared with others. The recording will be used to collect information on questions relevant to the project. Specific statements or quotes may be included in the evaluation report. However, all the information and statements will remain anonymous.

You have an option to opt out of any specific question asked during the meeting.

I would like to seek your permission to record the session before the commencement of today's meeting. Please let me know if there are any issues or conflict of interest.

List of Questions for discussion with probes as relevant to the stakeholders

1. Can you tell me about the AFP notification process in Queensland?

Probe 1: Is it simple or complex to report AFP cases in Queensland?

Probe 2: Is there any duplication or inefficiencies that you can identify?

2. Have you been involved in the notification process of AFP?

You mentioned you have been involved in the notification process of AFP.

If yes, is the notification of a AFP case to Queensland Health (Public Health Units or Communicable Disease Branch) within 24 hours of diagnosis?

Probe 1: Is the notification of cases to Queensland Health always on time or often delayed?

Why do you think the notification is on time/delayed?

Probe 2: What do you think can be done to improve the immediate notification process of AFP?

If not, do you think AFP is notified to Queensland Health in a timely manner (within 24 hours of diagnosis)?

Probe : Why do you think the notification is on time/delayed?

3. Do you think AFP notification in Queensland is useful or adds value over APSU/NERL/PAEDS notification process?

Probe 1: Could you please tell more on the usefulness or advantage of the notification in Queensland?

Probe 2: If AFP notification ceased, can you see any gaps in surveillance or risks that would develop?

4. Do you think AFP surveillance adds value when considered in the context of existing AFP/polio surveillance structures?

5. Are there any instances when NoCS AFP notifications contributed to taking public health actions?

Probe: Could you please share your experience when it has been useful?

6. AFP is nationally co-ordinated by APSU/NERL/PAEDS, and Queensland is the only state where it is notifiable. Should AFP remain a notifiable condition in Queensland?

Probe: Why do you think AFP should or should not remain a notifiable condition in Queensland?

7. Can you see now or in the future a purpose for Queensland AFP notification data at the Commonwealth level?

8. How does NERL receive request for laboratory testing of samples?

Is there any duplication of request received for sample testing?

9. Are there any issues or weaknesses in the system (how could it be improved)?

Would it make a substantial difference if all jurisdictions had AFP as a notifiable condition?

10. What is the turnaround time from specimen collection to receiving samples from QLD laboratories and providing results by NERL? Do you know if this is different to other states/territories?

11. Is there any delay during request for specimen collection from QLD to receiving samples at NERL?

Probe: What could be the reasons for delay and what can be done to improve?

12. How often do we get request for the two-specimen collection from QLD and is it 24 hours apart?

13. How does Pathology Queensland receive request for laboratory testing of samples? Are all specimens collected in Queensland sent to Pathology Queensland? Is there any duplication of request received for specimen collection?

14. What is the turnaround time from specimen collection to sending samples to VIDRL and obtaining results from VIDRL?

15. Is there any delay during request for specimen collection to sending samples to VIDRL?

Probe: What could be the reasons for delay and what can be done to improve?

16. How often do we get request for the two-specimen collection and is it 24 hours apart?

17. Do you have any other comments to make on the AFP surveillance/notification in Queensland?

Probe: Any final comments

Thank you all for making time to meet today. I appreciate your valuable comments and feedback. The findings from our discussion will be disseminated as a report after the final evaluation of the surveillance system.

I hope it is ok if I remain in touch for further feedback and queries.

Chapter VI:

Lessons from the field and teaching activities

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1. Lessons from the field

This Chapter was a part of the Master of Philosophy in Applied Epidemiology (MAE) Program to demonstrate competency in peer-to-peer teaching of a topic learnt from the field. The teaching activity provided me an opportunity to share my experience of learning while undertaking an epidemiological study. This involved developing a lesson plan relevant to the study including providing a brief context of the topic; designing activities or exercises to test lessons learned from the session; engaging in peer-to-peer learning; and obtaining feedback on the teaching session. As this competency involved working in groups, I learned to actively participate in each other's sessions, engage in discussion and above all work together to schedule the sessions remotely at times that would suit all the participants.

All of us were enthusiastic to learn about different research projects unique to our field placements and provide feedback to each other. This activity was a great exercise to understand the challenges of teaching and learning. I have upskilled my teaching ability by being specific and relevant to the topic, engaging with participants in an interactive manner, and completing teaching objectives within a short, allocated time.

The lesson from the field was useful to understand the concepts of vaccine efficacy and effectiveness and apply different epidemiological study designs in estimating vaccine effectiveness. The topic was developed to meet the following learning objectives:

- Differentiate vaccine effectiveness and vaccine efficacy
- Understand various study designs used in measuring vaccine effectiveness
- Identify confounding factors and bias associated with the study designs

Understanding an epidemiological concept of vaccine efficacy and effectiveness

1.1. Introduction

Vaccines currently in use have gone through many years of development, testing and trials until safe for administration in humans. Vaccines are developed based on various platforms such as live-attenuated vaccine, killed vaccine, DNA vaccine, mRNA vaccine, and sub-unit vaccine. They are then tested in an animal model (pre-clinical) for immune responses, inhibition of pathogens and adverse effects. Pre-clinical testing is followed by different phases of clinical trials, including randomised controlled trials in the later stages of development (Figure 1). The phases can overlap in an accelerated process for the development of a vaccine against a disease that requires immediate control and prevention (1).

- Phase 1: Tested in a few participants for immune responses, dose, and safety.
- Phase 2: Tested in hundreds of participants (different demographics) for immune responses, dose interval, and safety.
- Phase 3: Tested in thousands of participants for safety and efficacy, commonly using a randomised, controlled trial.

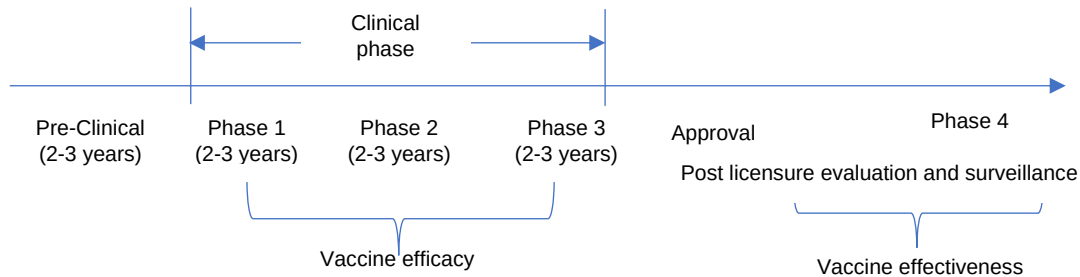


Figure 1. Timeline in the development of vaccine for the therapeutic use and stages at which vaccine efficacy and vaccine effectiveness are measured (1)

Vaccine efficacy

It refers to the percent reduction in rate of incidence of disease in a vaccinated group compared to an unvaccinated group under controlled conditions. It is calculated by comparing the number of cases of disease in the vaccinated group versus the placebo or inactive group (2).

Vaccine effectiveness

It is the measurement to determine the reduction in clinical outcomes after the implementation of a vaccination program in the population or “real world” setting (causal effect of vaccine on risk of disease) (2, 3).

Vaccine impact

It refers to the reduction in incidence of disease in the overall population due to vaccination of individuals in the population. The effect can be direct due to vaccination or indirect due to ‘herd protection’. It is determined by vaccine coverage, effectiveness, population size, structure, and access to health care and evaluated using active surveillance programmes comparing the incidence of disease before and after implementation of immunisation program (2). Vaccine impact can be measured through a range of outcomes such as incidence of disease, hospitalisation, and deaths.

1.2. Methods of estimating vaccine effectiveness (VE)

a) Cohort study design: Cohorts are selected based on the exposure status of individuals and followed over time to evaluate for the outcome of interest. The study involves separation of individuals into vaccinated and unvaccinated groups (cohorts) followed by identification of the individuals with the outcome of interest such as presence of a disease or hospitalisation due to a disease.

Benefit: The study can directly estimate incidence rates and the burden of a disease in the vaccinated and unvaccinated populations, which can easily be communicated to policy makers (4).

$VE = (1 - RR) \times 100$ (RR: Relative risk)

RR: Risk of disease among vaccinated group/Risk of disease among unvaccinated group

RR is also determined as incidence rate ratio based on incidence rates.

b) Case-control study design: The study involves identification of individuals with outcome of interest (case) and those without the disease (control). Information on vaccination history as exposure is then obtained for the cases and controls.

Benefit: Random selection of controls matched on similar co-variates (age and residence) with cases can remove selection bias (4).

$VE = (1 - OR) \times 100$ (OR: Odds ratio)

OR= odds of exposure (vaccination) among cases/odds of exposure (vaccination) among controls (Odds defined as probability that an event will occur divided by the probability that the event will not occur).

Odds of vaccination among cases=vaccinated case/unvaccinated case

Odds of vaccination among controls=vaccinated controls/unvaccinated controls

c) Test-negative: The study includes all persons who seek care for a defined set of symptoms resulting in a common diagnostic test, who are then categorised with positive test or negative test results. This is similar to case control study, where outcome is not known prior to selecting participants.

Benefit: Individuals in the comparison groups have similar health seeking behaviour or access to facilities for the disease of interest. It also reduces biases due to differences in community-level variations in vaccine coverage (4). Data on tests results are already available and need not be collected prospectively.

$$VE = (1 - OR) \times 100$$

d) Screening method: Vaccine effectiveness is measured by comparing the proportion of cases vaccinated (PCVA) with the proportion of population vaccinated (vaccine coverage) (PPV) (4).

$$VE = 1 - [PCVA/(1 - PCVA)]/[PPV/(1 - PPV)] \times 100 \text{ (5, 6)}$$

1.3. Questions for exercise

Question 1. What does it mean when efficacy of a vaccine is 80%?

It means that among participants of a clinical trial, individuals who received the vaccine was at 80% lower risk of developing disease compared to individuals who received placebo or an inactive treatment (unvaccinated group).

Question 2. What does it mean when vaccine effectiveness is 90%?

It means that the vaccine reduces the risk of a disease outcome by 90% among the vaccinated population when compared to the unvaccinated population.

Question 3. A vaccine effectiveness study against shingles was conducted among 70 year olds in Australia in 2021. There were 200 vaccinated individuals and 20 of them developed shingles. Whereas of the 205 unvaccinated individuals, 80 of them developed shingles. Calculate vaccine effectiveness for a shingles vaccine based on a cohort study design and interpret the result.

Risk of shingles in vaccinated= Shingles in vaccinated/Total vaccinated= 20/200

Risk of shingles in unvaccinated= Shingles in unvaccinated/Total unvaccinated=80/205

Risk ratio=(20 X 205) / (80 X 200)=0.25

VE=(Risk among unvaccinated group-risk among vaccinated group)/(risk among unvaccinated group)

Or VE= 1-0.25 X 100=75%

Vaccine effectiveness is interpreted as the proportionate reduction in disease among the vaccinated group. So, a VE of 75% indicates a 75% reduction in shingles occurrence among

the vaccinated group, or the vaccinated group experienced 75% fewer shingles episodes than they would have if they had not been vaccinated.

A risk ratio of 0.25 means the risk of shingles among the unvaccinated group was 4 times (1/0.25) higher compared to the vaccinated group.

Question 4. A case control study was conducted to determine varicella vaccine effectiveness among children aged older than 12 months. Calculate vaccine effectiveness with the following observation and interpret your result?

	Varicella	Non-case	Total
Vaccinated	20	130	150
Unvaccinated	60	85	145
Total	80	215	295

Odds ratio= Odds of varicella vaccination among varicella cases/Odds of varicella vaccination among non-case

Odds ratio= $(20 \times 85) / (130 \times 60)$

VE= $1 - 0.21 \times 100 = 79\%$

It indicates a 79% reduction in varicella occurrence among the vaccinated group, or the vaccinated group experienced 79% fewer varicella than they would have if they had not been vaccinated. Here the OR of 0.21 means the odds of being vaccinated was 4.8 times (1/0.21) among control group (non-cases) than among cases.

Question 5. Calculate vaccine effectiveness for a diphtheria vaccine based on screening study design with the following observation and interpret your result?

There were 50 individuals vaccinated against diphtheria among 200 diphtheria cases in a city. The population of the city was 60,000 and 40,000 individuals were vaccinated.

Proportion of diphtheria cases vaccinated= Number of diphtheria cases vaccinated/total number of diphtheria cases

Population vaccinated (coverage)= number of individuals vaccinated/total population

VE = $1 - [PCV / (1 - PCV)] / [PPV / (1 - PPV)] \times 100$

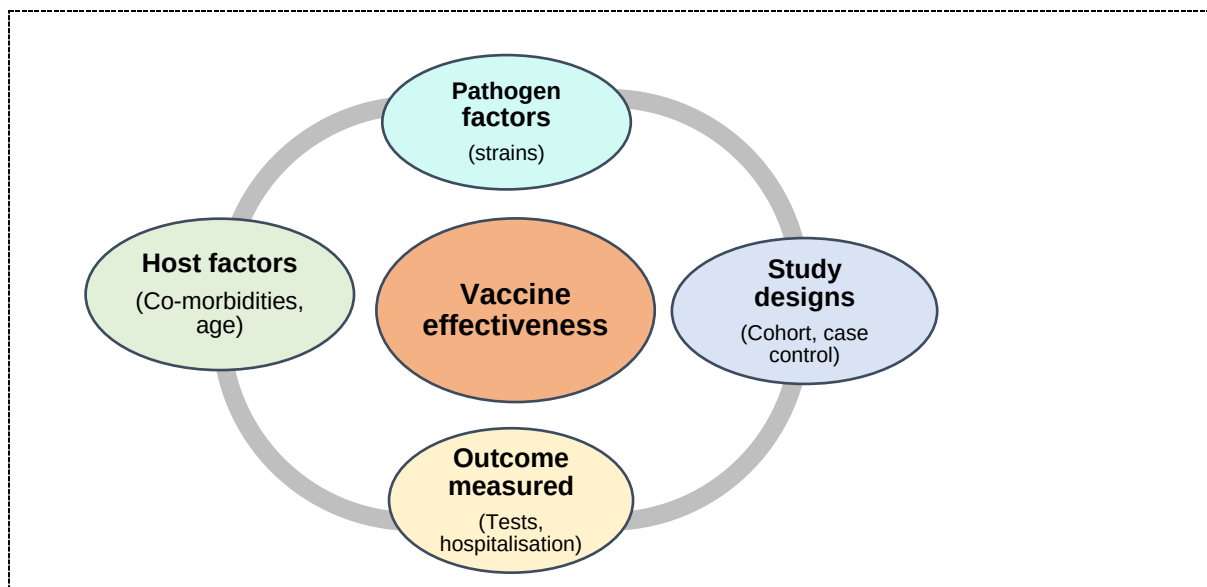
VE= $1 - [(50/200) / (1 - 50/200)] / [(40,000/60,000) / (1 - 40,000/60,000)] \times 100 = 83\%$

Reduction in diphtheria occurrence among vaccinated group was 83%.

Question 6. Can you measure vaccine effectiveness based on a case-series study? Please explain why or why not.

A case series study is a descriptive study that follows a group of patients (only cases) who have a similar diagnosis over a certain time period. A case-series study does not have a comparator group and relative risk or odds for the vaccination as exposure cannot be calculated. No causal inferences should be made from case series regarding the efficacy /effectiveness of the investigated treatment/interventions (7). However, if a case series study includes data on vaccination status, depending on the availability of vaccine coverage data, vaccine effectiveness can be determined by screening method.

Question 7. What factors can affect the results of vaccine efficacy and effectiveness studies?



Question 8. Discussion points (Group discussion during presentation)

A. How would you determine which study designs to use?

- Frequency of occurrence of a disease (e.g., case control for rare disease that would require small sample size)

- Availability of resources (for recruitment of participants, duration) and data sources (access to registry, disease notifications, laboratory database)

B. What are the challenges in conducting vaccine effectiveness studies?

- Reliability of data sources
- Availability of data sources
- Capacity for data linkage

C. What are the potential biases and how would you address biases in estimating vaccine effectiveness?

Cohort study: Differences in healthcare seeking behaviour can be a confounder which results in selection bias (people who seek health care are more likely to be vaccinated).

The confounding effect due to health seeking behaviour or access to health care can be determined by stratification into vaccinated or unvaccinated in previous year or vaccination against similar disease. Adjusted vaccine effectiveness can then be determined by combining (pooling) strata specific risks.

Case-control: Distribution of vaccination may be different between cases and controls. It can be addressed by adjusting during statistical analysis such as by residential region and age. Likewise, the manner in which vaccination status is obtained can result into information bias due to misclassification. It is preferable to use similar source of information for determining vaccination status for both cases and controls such as a registry.

Test-negative: Possible bias due to unknown co-morbidity in patients can influence influenza vaccination, risk of respiratory infections and hospitalisation. Chronic medical conditions can increase the risk of influenza related hospitalization and people with chronic medical conditions are likely to be vaccinated (4). Medical history/co-morbidities can be included as co-variates and adjusted during analysis. There is a possible measurement bias depending on sensitivity and specificity of tests. It can be minimised by considering test results from similar validated assays or test methods.

Screening method: The method is dependent on accurate and valid data on vaccine coverage in the source population, which may differ from the general population because

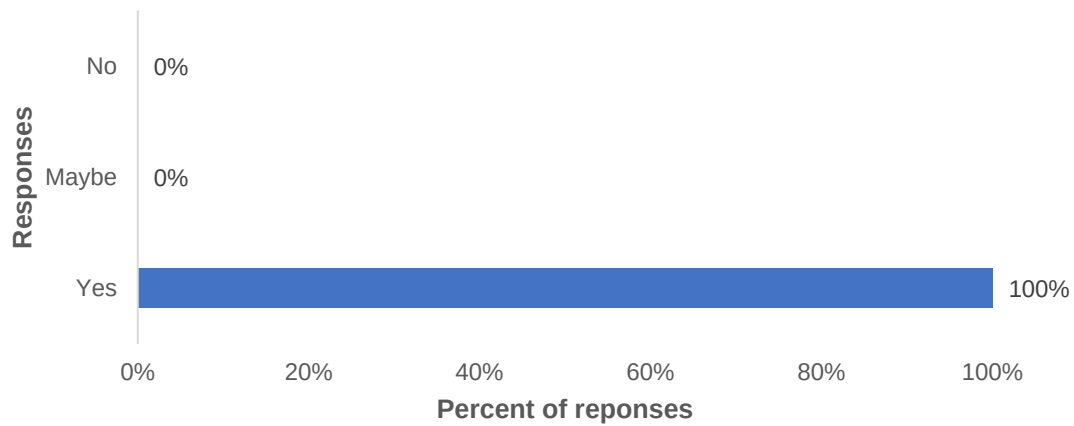
of differences in healthcare seeking behaviour or health care access (4). Estimation of coverage based on registry data is preferable compared to doses of vaccine administered in a population.

D. What are the key co-variables used in vaccine effectiveness studies and why?

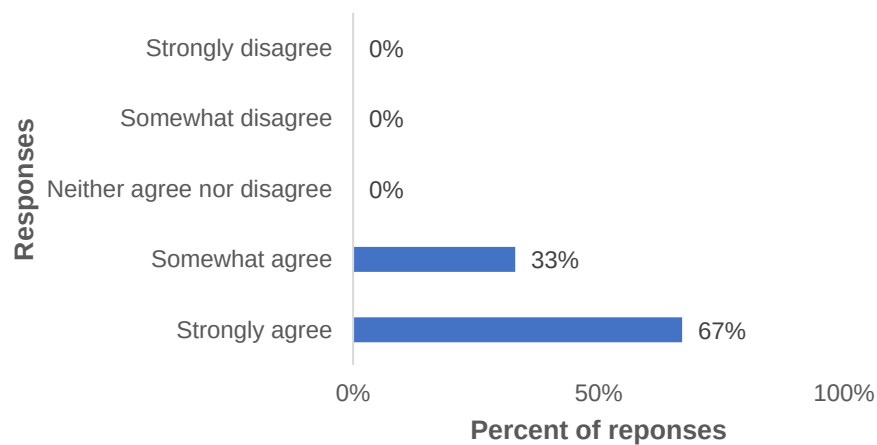
Co-variables	Comments
Age	Risk of infection and vaccine coverage varies by age
Sex	Access to health care specially in low resource settings
Ethnicity	Health care access and equity
Date of Onset	Determines person-time risk
Calendar-time	Affects vaccine uptake based on seasonality of disease
Vaccination history	Determines access to health care facilities and effectiveness due to previous vaccination
Co-morbidities and immunocompromised status	Influences disease outcome and receipt of vaccine for prioritised individuals. People with chronic disease likely to receive influenza vaccine (confounding by indication).
Socio-economic status	Affects health seeking behaviour and access to available vaccines
Pregnancy	Certain vaccines may not be safe or are recommended during pregnancy

1.4. Feedback from lesson from field participants

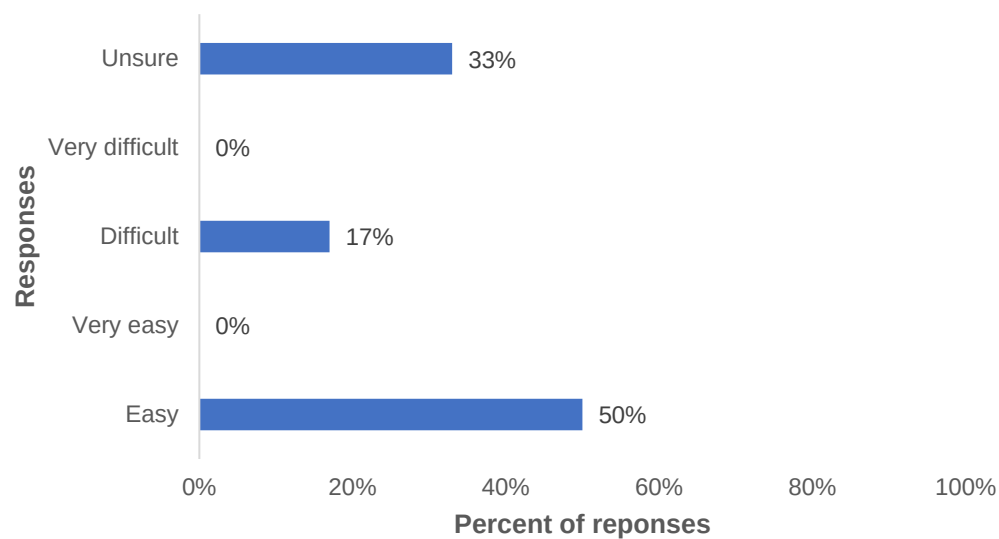
Q1 - Did the session meet the learning objectives?



Q2 - The session was interactive and engaging!



Q3 - Was the topic difficult or easy to understand?



2. Teaching field epidemiology

During the MAE Program I was also required to demonstrate competency in teaching first year MAE scholars. I was allocated to co-ordinate with five other scholars from my cohort to teach on a topic “An outbreak of arboviral infection in East-Arnhem land” on 20 February 2023. I was assigned to teach on the specific topics related to arboviruses, arboviral surveillance, line list, descriptive epidemiology, epi curve, and analysis of epi curve (Only selected slides shown below).

An outbreak of arboviral infection

This teaching session was a group activity and involved working with peers. I worked together to develop a lesson plan that would meet the given learning objectives. We undertook this task by assigning specific sections among us to cover the teaching content. In addition, providing feedback to each other's content before teaching was helpful to make the learning process simple and easy to understand. This activity was well received by the first-year students. Working in a team was satisfying to be able to teach the topic in an interesting manner. I have learned that practicing presentation is helpful to be comfortable and confident. Above all, including group activities after the completion of each learning objectives was useful to make the teaching and learning sessions interactive and engaging.

2.1. Presentation slides from my teaching

Australian National University

Arboviruses

- **Arthropod-Borne Viruses**
 - Arthropoda – segmented invertebrates with jointed legs
 - Blood-feeding behaviour of biting arthropods
 - Viruses

Sources: Milfi et al. International Journal of Molecular Sciences (2019) Prionex

Arboviruses

Single-stranded positive-sense RNA	Single-stranded negative sense RNA	Double-stranded RNA
Family: <i>Togaviridae</i> Genus: <i>Alphavirus</i> ⁴¹ Family: <i>Flaviviridae</i> Genus: <i>Flavivirus</i> ⁴¹	Family: <i>Bunyaviridae</i> Genus: <i>Orthobunyavirus</i> ⁴¹ <i>Nairovirus</i> <i>Phlebovirus</i> <i>Tospovirus</i> Family: <i>Rhabdoviridae</i> Genus: <i>Vesiculovirus</i> Family: <i>Orthomyxoviridae</i> Genus: <i>Thogotovirus</i>	Family: <i>Reoviridae</i> Genus: <i>Orbivirus</i> <i>Coltivirus</i> ⁴¹

Source: GY et al. Clinical and Experimental Vaccine Research 3 (2013)

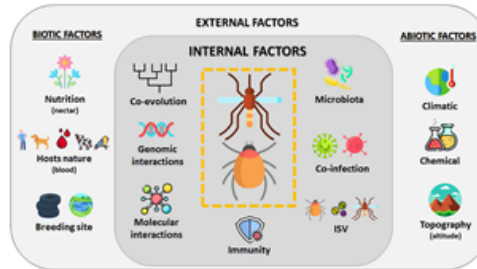
Hexapods Arachnids

Arboviruses

Common arboviruses and vectors

Virus Family	Virus Genus	Virus	Vector Species
Togaviridae	Alphavirus	Barmah Forest virus	Mosquitoes (Aedes and Culex sp)
	Alphavirus	Ross River virus Chikungunya virus	Mosquitoes (Aedes sp)
	Alphavirus	Sindbis virus	Mosquitoes (Culex sp)
Flaviviridae	Flavivirus	Dengue Virus	Mosquito (Aedes sp)
		Zika Virus	
		Yellow Fever virus	
	Flavivirus	West Nile Virus	Mosquito (Culex sp)
		Japanese Encephalitis Virus	
		Murray Valley Encephalitis Virus Kunjin virus	

Factors influencing pathogen transmission by a vector



Source: VM et al., *Frontiers in Microbiology* (2021)

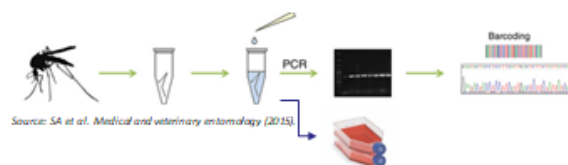
Arboviral Surveillance

Vector (entomological) surveillance

- Egg/mosquito trapping (mosquito abundance)
- Mosquito types
- Viruses in mosquitoes



Whole grinds of collected mosquitoes tested – cell culture, molecular methods



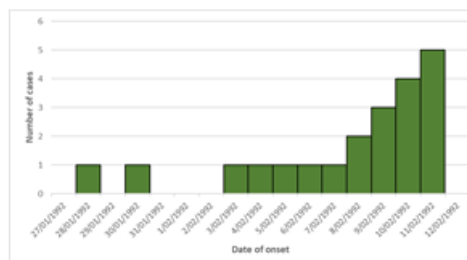
Case study: Mosquito density surveillance weekly by trapping;
Mosquito traps (12-13 Feb) – 2,830 mosquitoes

Descriptive epidemiology

- Observational
- Define population and disease
- Describe by person, time and place
- Measure disease trends
- Compare with known indices
- Generate hypothesis
- Monitor public health policies

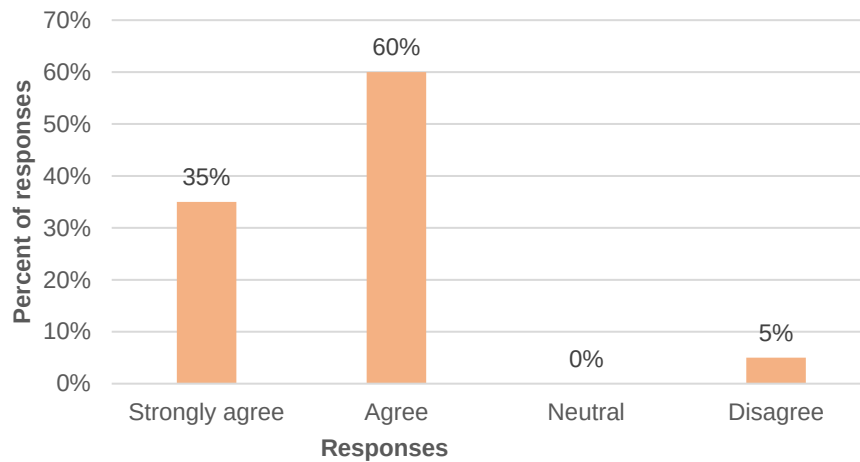
Activity

- Draw an epi curve using the given list of case study (5 minutes)
- Interpret the epi curve
 - ✓ Identify the pattern of spread
 - ✓ Assess the magnitude
 - ✓ Evaluate time trends
 - ✓ Examine outliers
 - ✓ Estimate the exposure period

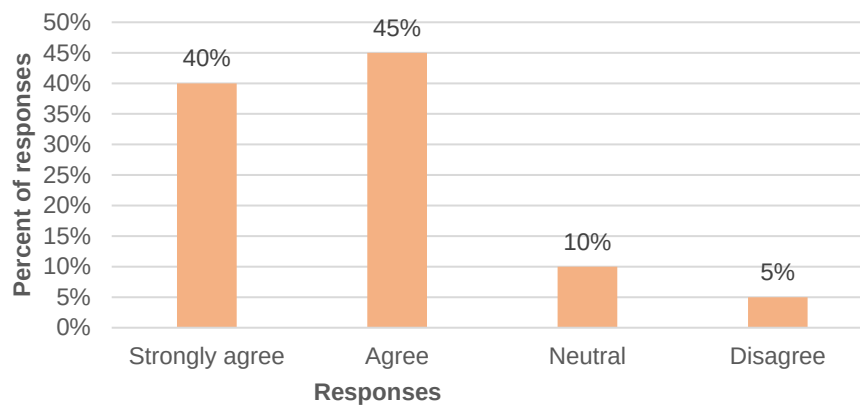


2.2. Feedback from first year scholars

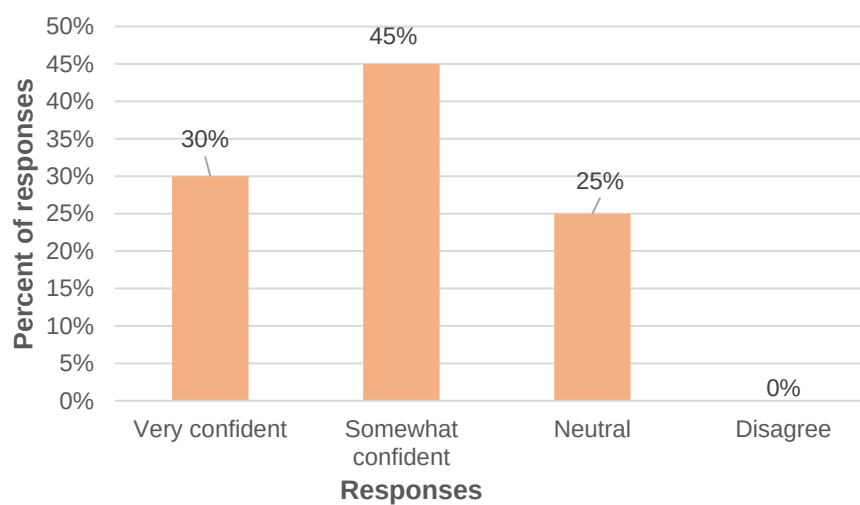
The lesson met the learning objectives



The lesson was useful



Rate your confidence: epi curves



3. References

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2. Australian Government Department of Health. Influenza vaccine efficacy, effectiveness and impact explained ;Internet]. Canberra: Australian Government Department of Health. 2018 [cited 2022 Aug 01]. Available from: [https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/\\$File/Vacc-efficacy-effect-impact-Oct18.pdf](https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/Vacc-efficacy-effect-impact-Oct18.pdf)
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4. World Health Organization. Evaluation of influenza vaccine effectiveness [Internet]. Geneva: World Health Organization. 2017 [cited 2022 Jun 06]. Available from: <https://apps.who.int/iris/bitstream/handle/10665/255203/9789241512121-eng.pdf>.
5. Cohen AL, Taylor T, Jr., Farley MM, Schaffner W, Leshner LJ, Gershman KA, et al. An Assessment of the Screening Method to Evaluate Vaccine Effectiveness: The Case of 7-Valent Pneumococcal Conjugate Vaccine in the United States. *PLOS ONE* [Internet]. 2012 Aug [cited 2022 Jun 6];7(8):e41785. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411566> DOI: 10.1371/journal.pone.0041785
6. Farrington CP. Estimation of vaccine effectiveness using the screening method. *Int J Epidemiol* [Internet]. 1993 Aug [cited 2022 Jun 07];22(4):742-6. Available from: <https://academic.oup.com/ije/article-abstract/22/4/742/664122> DOI: 10.1093/ije/22.4.742
7. Kooistra B, Dijkman B, Einhorn TA, Bhandari M. How to Design a Good Case Series. *JBJS* [Internet]. 2009 May[cited 2022 Jun 09];91 suppl 3:21-6. Available from: https://journals.lww.com/jbjsjournal/fulltext/2009/05003/how_to_design_a_good_case_series.5.a.spx DOI: 10.2106/JBJS.H.01573

Chapter VII:

Other public health activities and experiences

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1. Introduction

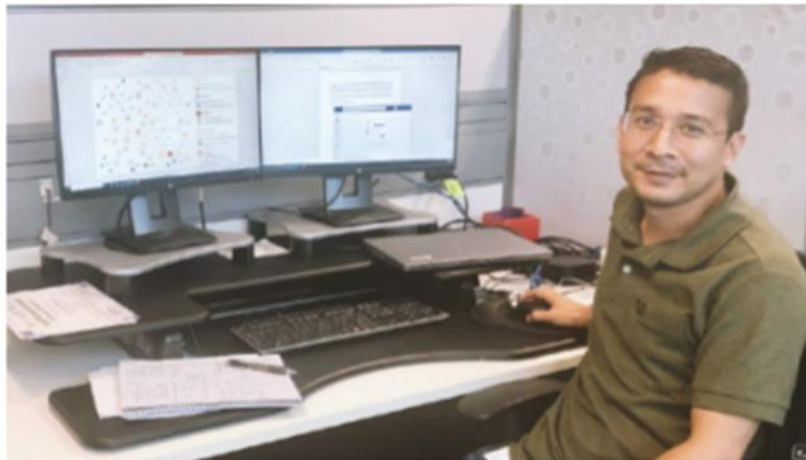
I had several opportunities to be involved in other public health activities in addition to the completion of the major competencies at my field placement. These included experience at a public health unit, participating in other departmental activities, and presenting my research projects to stakeholders. Such experiences were invaluable to gain a broader understanding of public health service and to engage in translating knowledge to practice.

2. Placement at the Metro South Public Health Unit, Queensland Health

I investigated COVID-19 cases infected with a variant of the Omicron strain in Queensland. I was based at the Metro South Public Health Unit, Queensland Health from 24 April to 19 May 2023 to undertake this work. I wrote a lay summary based on my experience, which was published as a research story on the ANU NCEPH website.

🏠 » Research » Research stories » Investigating a COVID-19 cluster: my field experience at a public health unit

Investigating a COVID-19 cluster: my field experience at a public health unit



19 SEPTEMBER 2023

Second-year *Master of Philosophy in Applied Epidemiology* Scholar [Ashish Shrestha](#) embarked on a field epidemiology training placement in Queensland. Below is a glimpse into his journey, as reported by Ashish Shrestha.

My field epidemiology training placement is at the Communicable Diseases Branch, Queensland Health.

As a part of my training, I have had an opportunity to investigate COVID-19 cases infected with a variant of the Omicron strain in Queensland.

These cases were identified after weekly monitoring of the genetic code of the virus that causes COVID-19 using a technique called whole genome sequencing. A majority of them were hospitalised patients.

To undertake this work, I was based at the Metro South Public Health Unit, Queensland Health, for four weeks from late April to mid-May this year.

As part of my MAE training, I was actively involved in leading this investigation, from developing a questionnaire and interviewing cases to identifying sources of infection. It was a great opportunity to understand the application of whole genome sequencing in epidemiology and to apply my skills to collate and analyse evidence collected through various sources.

I learned to overcome challenges in communicating with cases and their family members. Lessons learned were the importance of clear communication, using lay terms in describing the situation to the cases, communicating with empathy – and doing all of these things whilst obtaining information in a short time period.

My study determined that with this cluster, ongoing transmission of SARS-CoV-2 in the community was also matched with increased risk of transmission in high-risk settings, such as hospitals. This highlighted that community cases may be a marker of transmission in other settings and of the importance of infection and prevention control measures to minimise transmission to vulnerable patients.

Following up on this cluster was a great opportunity to understand the public health system in Queensland beyond my field placement.

An interesting learning experience at the public health unit was to observe the coordination and teamwork between the communicable diseases and environmental health teams. I learned about risk assessment and risk communication, foodborne and cancer cluster investigations, environmental health compliance, and mosquito surveillance.

As the public health unit was co-located with the public health laboratory, I had an opportunity to better understand whole genome sequencing results for my investigation from the team there.

I also had the chance to present one of my earlier projects on a foodborne illness to the public health professionals at the public health unit.

The four weeks I spent at the unit have provided me with a variety of experiences to explore and understand the wider context of the face-to-face public health system in Queensland.

Available at: <https://nceph.anu.edu.au/research/research-stories/investigating-covid-19-cluster-my-field-experience-public-health-unit>

3. Supported OzFoodNet Queensland in an outbreak investigation

An outbreak of *Salmonella* Typhimurium MLVA 03-13-07-09-523 associated with suspected baby cucumbers was alerted to OzFoodNet epidemiologists in December 2022. I assisted with interviewing a small number of the suspected cases in Queensland using a standard questionnaire. I collected data on different food items consumed by the cases during their illness to identify possible epidemiological links. Related to this, I also participated in the OzFoodNet multi-jurisdictional outbreak investigation teleconference. This experience was useful to understand the role of OzFoodNet in the investigation and management of food borne outbreaks.

4. Preliminary investigation of an acute public health problem

In Queensland, fourth dose pneumococcal vaccine coverage among Aboriginal and Torres Strait Islander children in September 2019 was lower compared to the estimates in prior and later years. The issue was identified in the Annual Immunisation Coverage Report 2021 published by National Centre for Immunisation Research and Surveillance. The coverage was 32% lower in September 2019 (48.3%) compared to the coverage in March 2019 (71.3%) and then increased to 81.6% in September 2021. There was no large decrease in coverage in other jurisdictions (the Northern Territory, South Australia, and Western Australia) at the same time point. I had an opportunity to be involved in this preliminary investigation to understand and identify possible reasons for the low vaccine coverage (Table).

Table. Possible reasons for decline in pneumococcal vaccine coverage and suitable methods for further investigation

Possible reasons	Methods
Decrease in supply of pneumococcal vaccine (PCV) leading to prioritisation of primary courses of PCV doses and deferring booster doses.	Semi-structured interview with vaccine providers, public health units and suppliers
Difficulties in accessing health care or vaccine providers during the period	Semi-structured interview with vaccine providers, public health units and suppliers Contact with family members by health contact centre
Misinformation/misunderstanding of the timing of required fourth dose required	Semi-structured interview with vaccine providers, public health units and suppliers, and investigate published schedules
Incorrect data entry of children receiving fourth dose of vaccine	Analyse data for vaccine coverage of other recommended vaccines at the same time points (12 months and 18 months) Vaccines administered at 12 months: Meningococcal B, MMR and at 18 months: Hepatitis A, MMRV, DTP
Changes in schedule for vaccination program	Investigate published schedules for vaccination program at different time points in Queensland

MMR: Measles Mumps Rubella, MMRV: Measles Mumps Rubella Varicella, DTP: Diphtheria Tetanus Pertussis

Preliminary analysis of data from September 2019 showed that majority of the children (55%) received fourth dose pneumococcal vaccine at 18-19 months. This differed to the recommended fourth dose at 12 months by Australian Immunisation Handbook (2, 4, 6, and 12 months). On further investigation we found that the Queensland National Immunisation Program Schedule, published in 2015, recommended the fourth dose at 18 months. The recommended age changed to 12 months in 2018 aligning with the Immunisation Handbook. The change in schedule for vaccination program could have led to confusion resulting in children missing the fourth dose.

5. Presentation to the collaborators and external stakeholders

5.1. National Centre for Immunisation Research and Surveillance (NCIRS)

I presented preliminary findings from my data analysis project on the epidemiology of varicella zoster virus in Queensland at the NCIRS meeting on 8th December 2022, organised by the Coverage, Evaluation and Surveillance team. The attendees included senior staff and students at NCIRS and my supervisors.

5.2. Polio Expert Panel (PEP)

I presented on the project proposal for the evaluation of surveillance of acute flaccid paralysis (AFP) in Queensland at the PEP meeting on 11th April 2023. The attendees included National AFP Surveillance Coordinator (National Enterovirus Reference Laboratory) and PEP Secretariat, representatives from the Australian Government Department of Health and Aged Care, and the Australian Paediatric Surveillance Unit.

5.3. OzFoodNet

I presented on the new notification pathway of STEC cases in Queensland at the OzFoodNet face to face meeting held on 30th May 2023 in Brisbane. The attendees included OzFoodNet epidemiologists from different jurisdictions, public health physicians, laboratory scientists, and other epidemiologists at Queensland Health.

5.4. Queensland Shiga-toxin producing *E. coli* (STEC) Guidelines Working Group

I participated in Queensland STEC Guidelines Working Group meetings. I had an opportunity to present on the findings from the investigation of STEC notifications in Queensland to the Working Group on 29th June 2023. The attendees were public health physicians from public health units of Queensland, scientists from pathology laboratories, and Queensland OzFoodNet epidemiologist.

5.5. Communicable Diseases Branch weekly notifications meetings

During my placement, I participated in weekly notifications meetings of the Communicable Diseases Branch. I also had an opportunity to share the findings from my data analysis project. The attendees included epidemiologists, public health physicians, and public health nurses of the branch.

6. Conference presentations

I gave oral presentations on the epidemiology of varicella zoster virus in Queensland, highlighting the use of intermittent enhanced surveillance data to understand impact of vaccination programs. These presentations were given at the Communicable Diseases and Immunisation Conference, Perth (19–21 June 2023) and the 1st SAFETYNET Conference, Canberra (12–15 September 2023). Of the 32 short oral presentations from different countries at the SAFETYNET Conference, I was awarded certificate of recognition for the Best Short Oral Presentation.



Presentation slides from the SAFETYNET Conference:

Queensland Health

Using Intermittent Enhanced Surveillance to Better Understand Varicella-Zoster Virus Epidemiology —
Queensland, 2010–2021

Ashish Shrestha, PhD
MAE Scholar (2022–2023)



Australian
National
University



Queensland
Government

Background

Varicella-Zoster (VZV): varicella (chickenpox) and herpes zoster (shingles)

Chickenpox

- More common in children and less severe than shingles¹
- Single dose chickenpox vaccine effective against reducing hospitalisation^{2,3,4}
- Single dose vaccine funded under National Immunisation Program (NIP) at 18 months of age (2005)⁵ – initially monovalent, then MMRV



Chickenpox vesicular lesions (ruptures and crusts)
(Image source: Royal Children Hospital Melbourne)

2

Background

Shingles

- Reactivation of VZV via dorsal root ganglia
- More common among older population (≥ 50 years old)⁶
- Live-attenuated shingles vaccine (ZVL) funded under NIP for people aged 70 years old; catch-up program for 71–79 years (2016)⁵
- Effectiveness of funded ZVL against incidence of shingles declines significantly in 5–10 years^{8,9}
- Adjuvanted recombinant shingles vaccine (RZV) provides protection for at least 10 years including frail elderly⁹



Shingles rash
(Image source: Queensland Health)

3

Aims

- Determine overall trend of VZV notifications in Queensland
- Determine clinical presentation in specific age groups using intermittent enhanced surveillance
- Understand changes in epidemiology following chickenpox and shingles vaccination programs

4

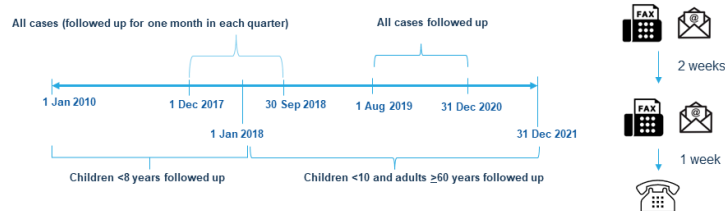


Methods

Study design: Case-series

Study period: 2010–2021

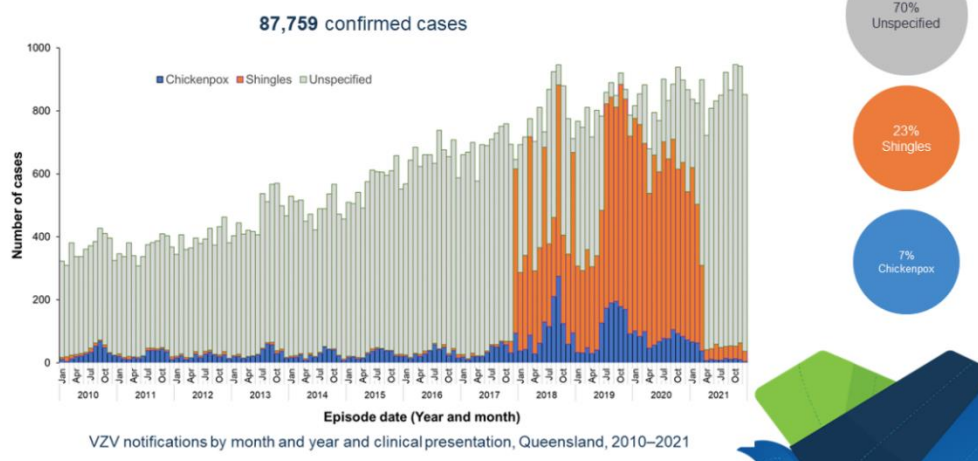
Data sources: Queensland Health Notifiable Conditions System (NoCS) – VZV notifications
Australian Bureau of Statistics – mid year Queensland population



5



Results



6



Results

Incidence rate ratio of VZV notifications in Queensland, adjusted by age and sex over the years 2010–2021

Characteristics	IRR**	P value	95% CI	
Year***	1.06	<0.001	1.05	1.06
Age group				
<1	Reference			
1-2	0.72	<0.001	0.61	0.83
3-4	0.82	>0.001	0.71	0.96
5-7	1.65	<0.001	1.43	1.90
8-9	1.97	<0.001	1.71	2.27
10-19	1.39	<0.001	1.21	1.60
20-29	1.44	<0.001	1.26	1.65
30-39	1.58	<0.001	1.38	1.82
40-49	1.61	<0.001	1.40	1.85
50-59	2.28	<0.001	1.98	2.61
60-69	3.17	<0.001	2.77	3.64
≥70	3.42	<0.001	2.98	3.93
Sex				
Male	Reference			
Female	1.08	<0.001	1.02	1.13

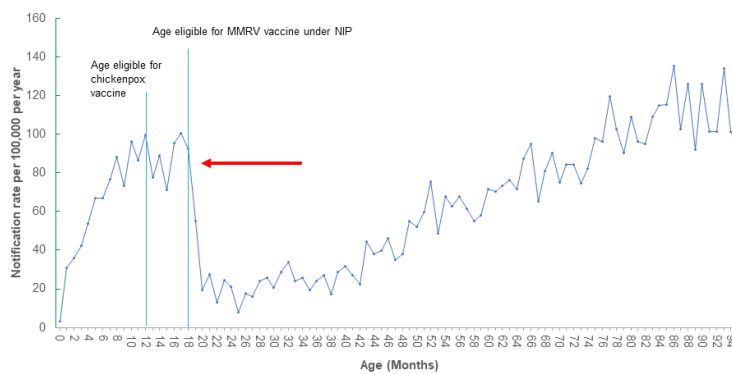
** IRR: Incidence rate ratio or rate ratio

7



Results

Impact of chickenpox vaccination program



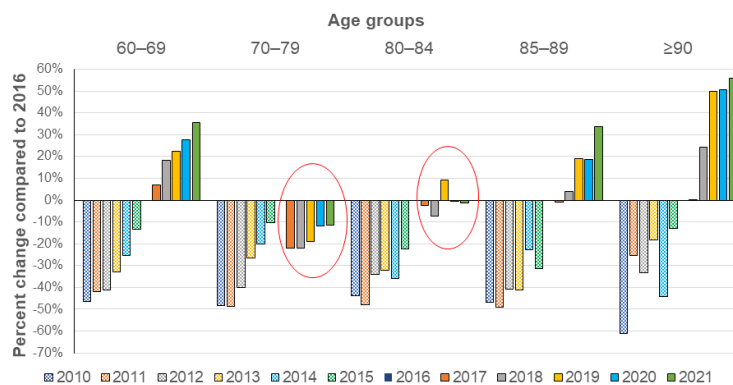
Chickenpox clinical presentation with enhanced surveillance among <8 years (2010–2021)

8



Results

Impact of Shingles vaccination program



Percent change in notification rate of shingles for each age group by year, compared to 2016

9



Summary

- VZV notification rate has increased over the years 2010–2021 in Queensland
- Intermittent enhanced surveillance useful to understand vaccine impact
- Impact of chickenpox vaccine and shingles vaccine
 - Decline in the rates from 18 months of age
 - Decrease in notification rate of shingles among 70–79 years of age after vaccination program
- Better control may be possible by introduction of a second dose of chickenpox vaccine in childhood and the use of more effective shingles vaccines^{8,10}

10



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Supervisors

A/Prof. Stephen Lambert
Dr Emma Field

Communicable Diseases Branch, Queensland Health

Mohana Rajmohan
Epidemiology and Research Unit
Data Services



National Centre for Epidemiology and Population Health (NCEPH) Australian National University



Email: ashish.shrestha@anu.edu.au

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7. Publications and peer-review

I submitted the following manuscripts for publication in peer reviewed journals:

- Assessing the impact of chickenpox and shingles vaccination using intermittent enhanced surveillance in Queensland, Australia (Journal: *Vaccine*, Submission date: 14/04/2023, Accepted date: 5/11/2023, Published date: 18/11/2023).
- Shiga toxin–producing *Escherichia coli* diagnoses from health practitioners, Queensland, Australia (Journal: *Emerging Infectious Diseases*, Submission date: 05/09/2023, Accepted date: 23/10/2023, Published date: 16/12/2023).

I have also had an opportunity to peer-review a research article on clinical trial of a live-attenuated varicella vaccine for the journal *Vaccine* (Report submitted: 25/05/2023).

8. Visit to public health laboratories

I visited public health laboratories of Queensland on 13th June 2022 at the Forensic and Scientific Services, Coopers Plains, Queensland and on 14th June 2022 at the Central Laboratory, Pathology Queensland, respectively. It was a great opportunity to meet key staff of the laboratories; understand role of various microbiology departments in pathology diagnosis, surveillance of infectious diseases, outbreak responses, and public health microbiology research; observe laboratory testing methods; and understand the process from sample collection, testing, interpreting results to notifying to public health unit/departments. It was an invaluable opportunity to know health professionals who were behind the scenes of surveillance of infectious diseases and outbreak investigation. This experience provided insight into importance of multi-disciplinary teamwork in public health and epidemiology.

Annex:

A literature review

Estimates of influenza vaccine effectiveness and efficacy, Australia

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1. Introduction

This annex is included in the thesis as a requirement of the Master of Philosophy in Applied Epidemiology Program for the competency in conducting a literature review on an epidemiological project. The review demonstrates my ability to search published journal articles in multiple databases based on the modified Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Relevant to my epidemiological study to estimate the influenza vaccine effectiveness in Queensland, a targeted literature review was conducted to understand study designs used for the estimation of influenza vaccine effectiveness and efficacy in Australia.

The primary aim of estimating influenza vaccine effectiveness is to determine reduction in clinical outcomes after the implementation of vaccination program in the population or 'real world' (causal effect of vaccine on risk of influenza) (1, 2). The clinical outcome can refer to incidence of disease, health care provider visit with disease or hospitalisation (2). However, the estimate may not remain same each year not only due to mismatch between vaccine composition and circulating pathogen in the environment but also due to different study designs and confounding factors considered in the studies. In order to update with the recent literature on influenza vaccines, the review was limited to publications with recruitment of study population in the last 10 years.

Unlike vaccine effectiveness, influenza vaccine efficacy refers to measurement of reduction of influenza incidence among selected groups of population after vaccination under controlled conditions as in randomised clinical trials (2). The estimates of influenza vaccine efficacy depend on the objectives of the study such as efficacy of the dosage and vaccine composition, which often report safety or adverse effects of the vaccines. In addition to the influenza vaccine effectiveness, the review aimed to understand recent influenza vaccine efficacy studies conducted in Australia in the last 10 years.

2. Methods

2.1. Influenza vaccine effectiveness

The keywords of interest were 'Influenza', 'flu', 'vaccine', 'immunisation', 'effectiveness', 'impact' and 'Australia'. Databases queried to identify research articles were PubMed, Scopus, and ANU SuperSearch using 'Advanced search' option (Table 1). The search was conducted in July 2022 and full articles were retrieved through the Australian National University (ANU) online library resource. The review process was based on the modified PRISMA of research articles (Figure 1). The EndNote files exported from each of the queried databases were

imported in EndNote Version 20 (Clarivate, UK). Duplicates were identified based on Author, Year and Title using 'Find Duplicates' option under 'References'. Duplicates with differences in formatting of author names and titles were manually identified and excluded.

Table 1. Databases and keywords searched for influenza vaccine effectiveness studies

Databases	Keywords with Boolean Operators and filters
PubMed	((Influenza[Title]) OR (Flu[Title])) AND ((Vaccine[Title]) OR (Vaccination[Title]) OR (Immunisation[Title])) AND ((Effectiveness[Title]) OR (Effect[Title]) OR (Impact[Title]) OR (outcome[Title])) AND ((Australia[Title]) OR (Australian[Title])) The search was limited to the publications in the last 10 years.
Scopus	(TITLE (influenza) OR TITLE (flu) AND TITLE (vaccine) OR TITLE (immunisation) AND TITLE (effective) OR TITLE (effectiveness) OR TITLE (impact) AND TITLE (Australian) OR TITLE-ABS-KEY (Australia)) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013))
ANU SuperSearch	((TitleCombined:(Influenza*)) OR (TitleCombined:(flu*))) AND ((TitleCombined:(Vaccine*)) OR (TitleCombined:(Vaccination*)) OR (TitleCombined:(Immunisation*))) AND ((TitleCombined:(effect*)) OR (TitleCombined:(impact*))) AND (TitleCombined:(Australia*)) The search was limited to peer reviewed, journal article and published in the last 10 years.

Abstracts of the articles were screened for the eligibility to be included for the review. The criteria for inclusion were articles with the objectives of estimating the influenza vaccine effectiveness by different epidemiological study designs. Articles focussed on cost-effectiveness of influenza vaccines; funding for immunisation; and estimates based on modelling and immune responses to influenza vaccines were excluded. The articles eligible for inclusion were searched for full text from the ANU online library. Articles with the study designs not including participants or population from the ten-year study period (2013–2022) were excluded. The articles to be included were reviewed for study design, population and study period, estimated vaccine effectiveness and study sites or data source.

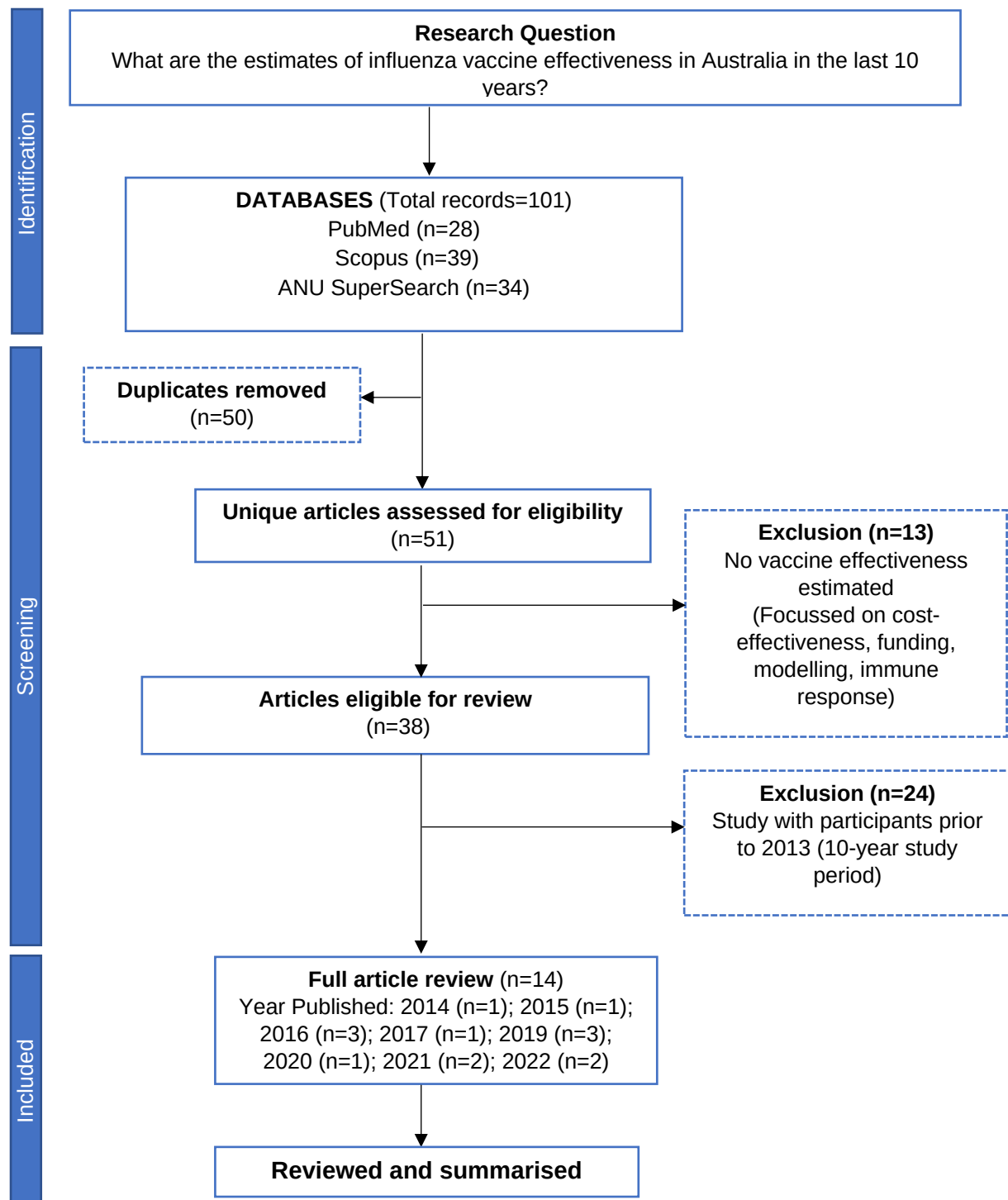


Figure 1. Modified PRISMA flowchart for review of articles on Influenza vaccine effectiveness in Australia, 2013–2022

2.2. Influenza vaccine efficacy

A separate search was conducted for the literature review of influenza vaccine efficacy in July 2022 using keywords and ‘Advanced search’ option in the databases (PubMed, Scopus, and ANU Supersearch) and limited to publications in the last 10 years (Table 2). Title of the articles

were screened to include articles from each database focussed only on influenza vaccine efficacy. Duplicates after merging list of articles from the databases were then removed as in Section 2.1. Abstract of the articles were screened to further exclude studies on influenza vaccine efficacy studied with other respiratory tract infection pathogens. Full text of the selected articles was retrieved from the ANU online library and the articles which included Australia as a site of study were reviewed further (Figure. 2). The review included participants recruited prior to the ten-year period (2013–2022) and multiple-sites (Australia and other countries) due to a limitation in number of studies.

Table 2. Databases and keywords searched for influenza vaccine efficacy studies

Databases	Keywords and Boolean Operators and filters
PubMed	(((Influenza[Title/Abstract]) AND (Vaccine[Title/Abstract])) AND (efficacy[Title/Abstract])) AND (Australia[Title/Abstract]) Influenza vaccine efficacy Australia (Basic search with no Boolean Operators)
Scopus	(TITLE-ABS-KEY (<i>influenza</i>) AND TITLE-ABS-KEY (<i>vaccine</i>) AND TITLE-ABS-KEY (<i>efficacy</i>) AND TITLE-ABS-KEY (<i>australia</i>)) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013)) AND (LIMIT-TO (AFFILCOUNTRY , "Australia"))
ANU	(SubjectTerms:(Influenza)) AND (SubjectTerms:(Vaccine*)) AND
SuperSearch	(SubjectTerms:(Efficacy*)) AND (SubjectTerms:(Australia*)) The search was limited to peer reviewed journal article.

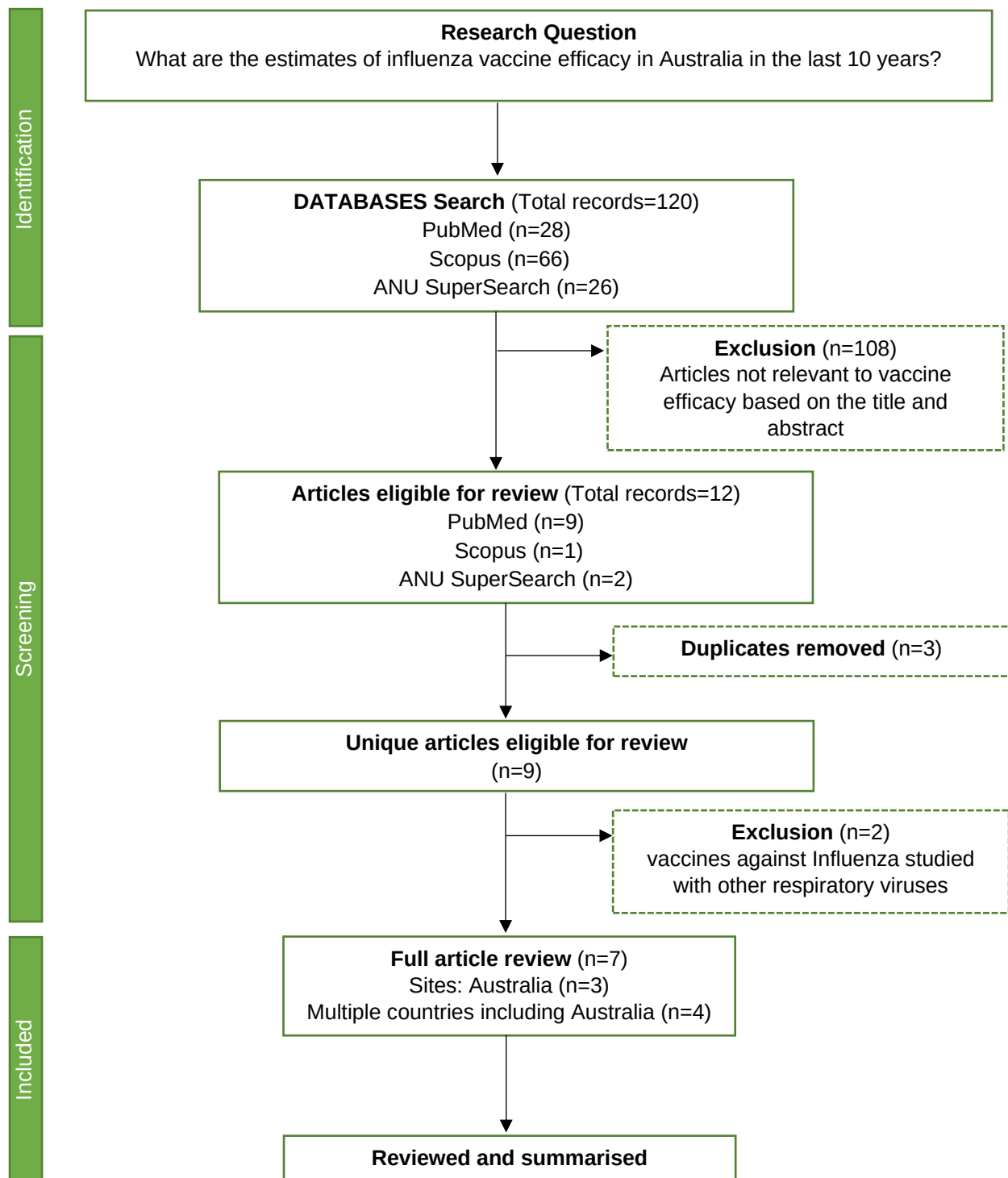


Figure 2. Modified PRISMA flowchart for review of articles on Influenza vaccine efficacy studies in Australia, 2013–2022

3. Results

A total of 51 articles were assessed for eligibility out of 101 retrieved articles estimating the influenza vaccine effectiveness in Australia. Thirteen articles did not include topic of interest and were excluded after screening of the abstract. The excluded articles discussed topics on cost effectiveness and impact of funding on vaccination (n=7), immunisation strategy and immune responses (n=2), vaccine uptake (n=2), and experimental studies (n=2). Of the remaining 38 articles, 24 were further excluded as the study population were before 2013, which did not meet the 10-year period criteria. Only 14 articles estimated influenza vaccine effectiveness and included study population from or between 2013 to 2022. Of these, 13 were based on test-negative and one case-control study designs. Absolute vaccine effectiveness (VE) as estimated in the reviewed articles ranged from 30.3–78.8% (Figure. 3).

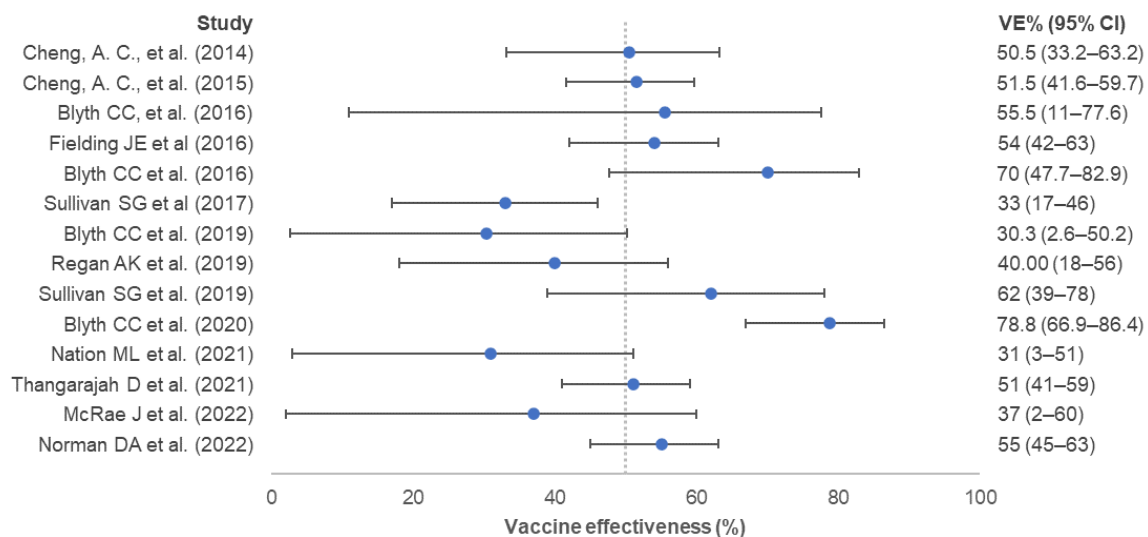


Figure 3. Absolute estimates of Influenza vaccine effectiveness

Likewise, only nine articles were assessed to be eligible for further review of influenza vaccine efficacy after excluding irrelevant articles and removing duplicates. Two of the nine articles were excluded as the study included efficacy estimation of influenza vaccine with other respiratory pathogens. Of the seven selected articles, only three articles included Australia as a primary study site and the remaining four included Australia as one of the multiple study sites. Six studies were based on randomised controlled trials (observer blinded=4, double-blinded=2) and one open-label single-arm. The studies differed in terms of vaccines being tested and specific conditions of the trials. Hence, specific range of vaccine efficacy estimate could not be determined.

4. Discussion

All the 14 studies included in this review for vaccine effectiveness were based on test-negative or case-control study designs. Of these, 13 studies recruited controls who tested negative to influenza and one other study recruited controls from immunisation register matched to cases. The case-control test-negative studies were based on a study population recruited from the Influenza Complication Alert Network (FLUCAN), the Paediatric Active Enhanced Disease Surveillance Network (PAEDS), the Australian Sentinel Practices Research Network (ASPREN) sentinel hospitals/sites and all were conducted during the seasonal influenza (April to November). This demonstrated the preference of case-control and test-negative study designs due to the known advantages of addressing bias resulting from differences in health-seeking behaviour between cases and controls and feasibility of recruitment of participants. Of the selected studies, four estimated pooled vaccine estimates based on the study population recruited over different years. A study based on matching controls to cases was based on study population included from notifiable conditions system and the Australian Immunisation Register. The estimates between studies varied, likely due to the different age groups of study population recruited, risk factors such as co-morbidities, outcome measured or due to actual differences between the circulating influenza virus not matching with the vaccine composition.

There were limited number of studies on influenza vaccine efficacy in Australia. All except one study were randomised clinical trials conducted at different phases. Vaccine efficacy was measured as influenza outcome confirmed by PCR, culture positive or seroconversion. The estimates also varied across the measured outcome in addition to the differences in vaccine type, adjuvants, dosage, and vaccine being tested on different population with specific conditions. Vaccine efficacy studies are prospective studies and often involves multiple site or countries for the clinical trials, which limits the number of specific studies of interest. Therefore, the review included studies which recruited participants outside the 10-year study period and from multiple countries including Australia.

5. Conclusion

A number of influenza vaccine effectiveness studies have been conducted in Australia over the last 10 years based on case-control study and test-negative designs. Although there are limitations, such a study design is preferable due to availability of information on participants' influenza laboratory testing result with vaccination history and smaller sample size required compared to cohort studies. Estimates of influenza vaccine effectiveness and efficacy can vary between studies and therefore should be compared and interpreted with caution.

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