INVESTIGATING VACCINE PREVENTABLE DISEASES AND THE COVID-19 PANDEMIC

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

November 2021

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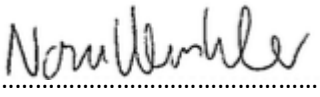
Originality statement

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial 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 acknowledgment is made in the thesis. Any contribution made to the research by others 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.

Signed 

Date: 29 October 2021

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Abbreviations and acronyms

ABS	Australian Bureau of Statistics
ACR	Australian Coordinating Registry
AHPPC	Australian Health Protection Principal Committee
AIHW	Australian Institute of Health and Welfare
AIR	Australian Immunisation Register
ATAGI	Australian Technical Advisory Group on Immunisation
CDNA	Communicable Diseases Network Australia
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
CRF	Case report form
DTPa	diphtheria-tetanus-acellular pertussis (child formulation vaccine)
dTpa	diphtheria-tetanus-acellular pertussis (reduced antigen formulation vaccine)
ECEC	Early Childhood Education and Care
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
FluCAN	Influenza Complications Alert Network
HDU	High dependency unit
HITH	Hospital in the Home
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

ICD-10-AM	The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modifications
ICPMR	Institute of Clinical Pathology and Medical Research
ICU	Intensive care unit
PAEDS	Paediatric Active Enhanced Disease Surveillance
PHAA	Public Health Association of Australia
PHEOC	Public Health Emergency Operations Centre
PHU	Public Health Unit
PIMS-TS	Paediatric Multisystem Inflammatory Syndrome–Temporally Associated with SARS-CoV-2
MCV1	Measles-containing vaccine (first dose)
MCV2	Measles-containing vaccine (second dose)
MMR	Measles-mumps-rubella
MMR2	Measles-mumps-rubella (second dose)
MMRV	Measles-mumps-rubella-varicella
NAT	Nucleic Acid Test
NCIMS	Notifiable Conditions Information Management System
NCIRS	National Centre for Immunisation Research and Surveillance
NHMD	National Hospital Morbidity Database
NIP	National Immunisation Program
NMA	National Mutual Acceptance
NNDSS	National Notifiable Diseases Surveillance System

NP	Nasopharyngeal
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCHN	Sydney Children's Hospital Network
SoNG	Series of National Guidelines
SPRINT-SARI	Short Period Incidence Study of Severe Acute Respiratory Illness
WHO	World Health Organization

Acknowledgements

I would firstly like to thank the National Centre for Immunisation Research and Surveillance (NCIRS) for giving me the opportunity of a field placement. I still can't believe my luck. I would like to give a huge thanks to Dr Beard, Dr Dey, Dr Quinn, Dr Pourmarzi, and A/Prof Lambert for their tireless commitment, patience, expertise, and guidance throughout my MAE experience. It is thanks to them that this thesis was possible. I would like to thank Prof Kristine Macartney for remarkable leadership at NCIRS through this particularly eventful period. I would like to acknowledge Dr Ben Polkinghorne, Prof Ross Andrews, and all the MAE faculty for their hard work in administering and delivering the program.

I would like to thank the MAE20 cohort – such an impressive and remarkable group of people. I'm privileged to be counted in your numbers.

I would like to thank Peter and Sue for their support and for their curiosity and interest. You have become epidemiologists-by-proxy through many long conversations about the pandemic. And last but not least, I would like to thank Tara. Like Nagy and Evie, and Peter and Eva before us, you are in my corner, and I am in yours.

Abstract

Vaccination is widely regarded to be one of the greatest public health achievements of the 20th century. While 2020 was the Year of COVID-19, 2021 is being regarded as the Year of the Vaccine, with vaccinations in the public spotlight, serving as a cornerstone of global pandemic management. This thesis contains work undertaken for the Master of Philosophy in Applied Epidemiology (MAE) while on placement at the National Centre for Immunisation Research and Surveillance (NCIRS) in 2020 and 2021. The MAE core requirements presented in this thesis cover four pillars of epidemiology: investigation of an acute public health problem or threat (outbreak investigation), public health data analysis, epidemiological study, and the establishment or evaluation of a surveillance system.

Chapter 1 describes my field placement, the experiences I had whilst on the MAE, and how I achieved the competencies for the program.

The outbreak investigation competency is fulfilled by my participation in the COVID-19 Schools Study, which ran across both 2020 and 2021. This was an active surveillance project carried out in all NSW schools and early childhood education and care (ECEC) services to quantify and characterise the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in these settings. I present some of the findings in Chapter 2, showing that while spread in educational settings was limited, a small number of outbreaks did occur and transmission within these outbreaks may have been facilitated by delayed outbreak recognition, very close or prolonged contact with a case, and specific high-risk transmission events. The risk of school and ECEC outbreaks may be mitigated by stay-at-home-if-sick messaging, school-based mitigation measures aimed at improving infection prevention and control, and restricting high-risk activities to times with low community incidence of disease.

In Chapter 3, I present a detailed analysis of national measles notifications, hospitalisations, and deaths from 2012 to 2019 which fulfilled the competency for conducting an epidemiological study. Australia was verified as having eliminated measles in 2014, but incidence almost doubled in the 2012 to 2019 period compared with 2000 to 2011. While the data presented in Chapter 3 support Australia's continuing elimination status, global progress towards elimination has stalled, and a global resurgence is expected as a result of increased immunity gaps due to the COVID-19 pandemic. Australia will need to remain vigilant, maintaining robust surveillance and high coverage of measles vaccination.

The MAE requirement of carrying out a public health data analysis project is demonstrated in Chapter 4, in which I report my analysis of two decades of national diphtheria notification, hospitalisation, and mortality data (1999–2019). Although still exceedingly rare, Australia has seen an increase in notified cases of diphtheria in the last decade, likely driven by a combination of a series of case definition changes occurring over the period and improvements in case ascertainment. It remains important to maintain high levels of vaccination coverage. In particular, pre-travel booster vaccination should continue to be encouraged.

A surveillance system evaluation project is presented in Chapter 5, in which I evaluated the COVID-19 and Paediatric Multisystem Inflammatory Syndrome–Temporally Associated with SARS-CoV-2 (PIMS-TS) components of the Paediatric Active Enhanced Disease Surveillance (PAEDS) system. The evaluation followed the Centers for Disease Control and Prevention's Updated Guidelines for the Evaluation of Public Health Surveillance Systems using a mixed methods approach, and provided recommendations for ensuring PAEDS can continue to continue to support Australia's national surveillance goals into the future.

Chapter 6 outlines teaching activities undertaken during my MAE and lessons learnt through such activities.

The work presented in this thesis represents my MAE activities at NCIRS, and a contribution to public health in Australia.

Chapter 1

Summary of field experience and MAE core requirements

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1.1 Field placement

My placement was at the National Centre for Immunisation Research and Surveillance (NCIRS) in Sydney, Australia. NCIRS was established in 1997 by the Australian Government to monitor vaccine-preventable disease (VPD) incidence and vaccination coverage as part of the Immunise Australia seven-point plan. It has collaborations at local, state and territory, national, and international levels, and across government, clinical, and academic sectors.

NCIRS' work has four main components, which encompass the complete lifecycle of vaccines: research, immunisation program support, knowledge translation, and monitoring and evaluation. I was situated within the Surveillance, Coverage, Evaluation, and Social Sciences team, with some time spent with the clinical research team while working on the COVID-19 School Study.

1.2 Core requirements

Investigation of an acute public health problem or threat

On 11 March 2020, two days after I commenced my field placement, I started work on a prospective cohort study to investigate SARS-CoV-2 transmission in schools and early childhood education and care services (ECECs), commissioned by NSW Health and led by A/Prof Nick Wood, Dr Archana Koirala and the clinical research team. The goal of this investigation was to quantify and characterise any school- or ECEC-based spread of SARS-CoV-2 among students and staff. As part of this investigation, I designed surveys, collated data from the Notifiable Conditions Incident Management System (NCIMS), participated in field serology collection days, wrote weekly reports to the Ministry of Health and lay summaries of the results at the end of each school term. Throughout 2020, we found that transmission within the education setting was rare in the context of the NSW outbreak, but a small number of outbreaks did occur. Transmission within these outbreaks may have been facilitated by delayed recognition, very close or prolonged contact with a case, and specific high-risk transmission events. The risk of school and ECEC outbreaks may be mitigated by stay-at-home-if-sick messaging, school-based mitigation measures aimed at improving infection prevention and control, and restricting high-risk activities to times with low community incidence of disease.

Design and conduct an epidemiological study

Under its funding agreement with the Commonwealth Department of Health, NCIRS delivers detailed reports on vaccine-preventable diseases as part of an ongoing series called the Australian Vaccine Preventable Disease Epidemiological Review Series. Since 2013, there have been several changes to measles immunisation policy, including a National Immunisation Program (NIP) schedule

change, and the introduction of the 'No Jab No Pay' policy. In 2014 Australia was certified as having eliminated measles. It was therefore decided that the 2021 Epidemiological Review would be on the topic of measles. I was the principal investigator of the study, which provided a detailed analysis of national measles notifications, hospitalisations, and deaths. We found that although measles remains rare in Australia, importations have increased, and vigilance is required to maintain elimination, through maintenance of high coverage of childhood immunisations and robust disease surveillance. A manuscript from this work has been accepted by *Communicable Diseases Intelligence* (*CDI*) for publication, and an abstract has been accepted for presentation at the Communicable Diseases and Immunisation Conference 2022.

Analysis of a public health dataset

Notified cases of diphtheria have re-emerged in Australia in recent years, resulting in a recommendation in the 2012–2015 NCIRS Vaccine Preventable Diseases Summary Report to investigate this increase with a detailed review. I was the principal investigator of the study, which reviewed and described national diphtheria notifications, hospitalisations, and deaths from 1999 to 2019. We found that although case notifications have increased, diphtheria is very rare in Australia, with better case ascertainment and notification, and changes in the national case definition likely contributing to the increased number of cases. High immunity across all age groups is required to prevent outbreaks in Australia and travel vaccination should be encouraged where indicated. A manuscript from this work has been accepted by *CDI* for publication.

Evaluation or establishment of a surveillance system

The Paediatric Active Enhanced Disease Surveillance (PAEDS) system is a hospital-based, sentinel surveillance system that was established in 2007 and adapted to collect data on paediatric COVID-19 and Paediatric Multisystem Inflammatory Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) cases in 2020. It has been identified as a key data source under goal 9 in the Australia National Disease Surveillance Plan for COVID-19 Version 2.0. Following the Centers for Disease Control and Prevention Updated Guidelines on the Evaluation of Public Health Surveillance Systems and using a mixed methods approach, I evaluate how PAEDS incorporated COVID-19 and PIMS-TS surveillance into its framework, its capacity to support Australia's national surveillance goals, and make recommendations.

Prepare a scientific manuscript for publication in a peer-reviewed journal

Manuscripts from the work on measles (Chapter 3) and diphtheria (Chapter 4) were accepted by *Communicable Diseases Intelligence:*

- Winkler NE, Dey A, Quinn HE, Pourmarzi D, Lambert SB, McIntyre P, Beard F. Australian vaccine preventable disease epidemiological review series: measles, 2012–2019. *Communicable Diseases Intelligence*. 2022 (Accepted).
- Winkler NE, Dey A, Quinn HE, Pourmarzi D, Lambert SB, McIntyre P, Beard F. Australian vaccine preventable disease epidemiological review series: diphtheria, 1999–2019. *Communicable Diseases Intelligence*. 2022 (Accepted).

I was also a contributing author on the following manuscripts:

- Macartney K, Quinn HE, Pillsbury AJ, Koirala A, Deng L, Winkler, N, et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. *Lancet Child Adolesc*. 2020; 4(11):807–816.
- Koirala A, Goldfeld S, Bowen AC, Choong C, Ryan K, Wood N, Winkler N, Danchin M, Macartney K, Russell FM. Lessons learnt during the COVID-19 pandemic: Why Australian schools should be prioritised to stay open. *J Paediatr Child Health*. 2021;57(9):1362-1369.

Communication to a lay audience

At the end of each school term in 2020, I co-authored lay summaries for the public on the findings of the COVID-19 School Study. These were published on the NCIRS website, with press releases from the Ministry of Health and Department of Education. The public summary from Term 3, 2020 is in Chapter 2 as an appendix.

Conference presentation

I gave the following presentation at the Australasian COVID-19 Virtual Conference:

- Factors contributing to SARS-CoV-2 outbreaks in four New South Wales educational settings. Public Health Association of Australia Australasian COVID-19 Virtual Conference, 8–10 December 2020.

Literature review

I conducted a focussed literature review related to Chapter 3 on the impact of the COVID-19 pandemic on measles vaccination coverage in the South East Asia and Western Pacific regions.

Teaching

I participated in the following teaching activities:

- Teaching to MAE21 during Course Block 3 on the topic of vaccine pharmacovigilance in the context of the start of the COVID-19 vaccine rollout
- Lessons from the Field with MAE20 on the topic of coverage estimates and birth cohorts based on historical vaccination schedules
- Facilitating a workshop for third year University of Sydney Applied Medical Science students
- Contributing to the design of a lecture on outbreaks of vaccine preventable diseases, and facilitating a tutorial on the Texarkana measles case study for the Vaccines in Public Health subject for the Sydney University Master of Public Health course

MAE coursework

I completed the following ANU subjects as required by the MAE

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

1.3 Additional courses and awards

Courses:

- NCIRS scientific writing workshop, 2021

Awards:

- NSW Research Impact Showcase for the COVID-19 Schools Study

1.4 Summary of MAE requirements

Table 1.1. Summary of MAE requirements included within the chapters of this thesis

Core requirements	Chapter				
	2	3	4	5	6
Response to an acute public health problem or threat	✓				
Design and conduct an epidemiological study		✓			
Analysis of a public health dataset		✓	✓		
Evaluate or establish a surveillance or other health information system				✓	
Literature review		✓			
Report to a non-scientific audience	✓				
Advanced draft of a paper for peer-reviewed publication		✓	✓		
Teaching activities					✓

Chapter 2

SARS-CoV-2 transmission in schools and early childhood education and care settings, New South Wales, 2020

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2.1 Prologue

Background

This chapter fulfils the MAE requirement to complete an investigation of an acute public health problem or threat. Three days into my field placement at the National Centre for Immunisation Research and Surveillance (NCIRS), the 2019 novel coronavirus was officially declared a pandemic by the World Health Organization (WHO). At the time, 118,000 cases and 4,291 deaths had been recorded across 114 countries, with Australia reporting 112 total confirmed cases and 3 deaths. On the same day as the pandemic declaration, NCIRS was engaged by NSW Health to commence enhanced investigations to characterise transmission of COVID-19 in selected school settings. We planned the study that day and recruitment of participants began the following evening. Over the following weeks, the study was expanded to also include passive surveillance of all NSW schools that had a confirmed case of COVID-19 attend while infectious.

When this investigation commenced, very little was known about COVID-19 in the school setting. The study contributed to a growing body of international evidence through publications, reports, and presentations. This Chapter was written in December 2020. It introduces the study through the lens of what was known about the topic at the start of the study, and discusses the findings in the context of what was learnt throughout the year.

My role

My role within the study team was initially to draft and create online REDCap survey software instruments to provide participants with information sheets, written consent forms, and a survey. REDCap is a web-based software for creating and managing surveys and databases. These required updating and tailoring as we recruited more schools and early childhood education and care (ECEC) facilities with different settings and needs. I monitored the Public Health Emergency Operations Centre (PHEOC) online communications board to identify new school/ECEC cases and liaised with the Operations team to obtain contact lists for each index case. Using these lists, I created clusters on the NCIMS, in collaboration with public health unit and PHEOC staff, to allow for more efficient follow up of school clusters and exportation of NCIMS data at the end of the follow up period. I also reviewed and collated the data weekly and I used these data to produce up-to-date reports for the Ministry of Health. I participated in the creation of public summary reports on the findings of the study at the end of each school term at the request of NSW Health, as well as a number of presentations for various audiences. I co-authored two manuscripts on the results of the study and

presented some of the results at the Public Health Association of Australia Australasian COVID-19 Virtual Conference.

Public health impact

This experience really was *applied* epidemiology with immediate public health impact. Our study directly informed state and national policies on school closure. The first public summary was published on the NCIRS and NSW Health websites on 26 April 2020, at a time when the debate about the safety of schools in Australia was at its height. The research was discussed in government press conferences at state and national levels and garnered significant media attention in major print and televised news outlets. It therefore played an important role not only in the formulation and adoption of government policies, but also in public confidence in those policies.

The findings of the study were published in *The Lancet Child and Adolescent Health* as well as in several public reports, and were presented in an NCIRS webinar, with further presentations to Communicable Diseases Network Australia (CDNA), United States Centers for Disease Control (CDC), the New South Wales (NSW) and Western Australia (WA) Ministries of Health, among others. Representatives from the study team were also involved in an international WHO working group on COVID-19 in schools. I presented these findings at the Australasian COVID-19 Virtual Conference in 2020.

Lessons learnt

Throughout this project, and particularly as it was the first project of my MAE, I learnt many technical skills, including study design, writing participant information sheets, using REDCap, designing surveys, the use of whole genome sequencing, data analysis and presentation, report writing, and writing and submitting a manuscript for publication.

Further to this, I learnt broader field epidemiology lessons about public communication of research. The first public summary was met with vigorous debate, among both the public and the scientific community. Through this experience I learnt valuable lessons about how to communicate research to a lay audience, including how to pitch the communication, and pre-empting likely misunderstandings. I also learnt about the political nature of public health research and the challenges that this represents for communication to the public.

Acknowledgements

I'd like to acknowledge the core schools study team, notably A/Prof Nick Wood, Dr Helen Quinn, Dr Archana Koirala, Dr Lucy Deng, Alexis Pillsbury, and Catherine Glover for their hard work and mentorship throughout the study. In particular I'd like to thank Dr Quinn for her guidance throughout the study. I'd like to acknowledge Prof Kristine Macartney for her leadership, and for her initiative in bringing me into the study. I'd like to acknowledge the wider NCIRS schools study team: Deidre Brogan, Nicole Dinsmore, Dr Andrew Dunn, Ajay Jadhav, Rosemary Joyce, Dr Rama Kandasamy, Kathryn Meredith, Lisa Pelayo, Laura Rost, Gemma Saravanos, and Evangeline Gardiner. Finally, I'd like to acknowledge the public health unit, laboratory, and PHEOC teams for their collaboration, including but not limited to: Dr Anthea Katelaris, Dr Shopna Bag, Dr Rebecca Rockett, and Paula Spokes.

2.2 Abstract

Background: When commencing this work in March 2020, the role of schools and early childhood education and care settings (ECECs) in COVID-19 outbreak propagation and factors associated with SARS-CoV-2 transmission in these settings was not well understood.

Methods: For the period 5 March to 25 September 2020, all school/ECEC related close contacts of a confirmed case of COVID-19 who attended any educational setting when infectious were followed for 28 days after their last exposure to the case. Results of testing (nucleic acid test [NAT] and serology) were monitored and any secondary cases were interviewed regarding their risk factors and possible exposures. Where outbreaks occurred in an educational setting, a thorough investigation of the outbreak was carried out to understand transmission within the setting.

Results: In total, 5790 contacts of 72 primary cases (24 staff and 48 students) from 65 educational settings (28 high schools, 20 primary schools, and 17 ECECs) were identified. Test results (NAT, serology, or both) were available for 4607/5790 (79.6%) contacts. A total of 51 secondary cases (secondary attack rate 0.9%), including 38 children and 13 staff, were detected in 14/65 (21.5%) educational settings. Three high schools and one ECEC experienced high transmission (≥3 secondary cases). Delayed outbreak recognition, high-risk events, and very close contact and mixing were factors that likely contributed to transmission in these four settings.

Conclusion: Secondary transmission within the school and ECEC setting was limited but variable. The risk of larger outbreaks in educational facilities may be reduced by stay-at-home-if-sick messaging, physical distancing and reducing mixing where able, and limiting higher risk activities to when community incidence of disease is low. These findings may be used to inform future studies and government policies on school closures.

2.3 Introduction

COVID-19 and its causative organism severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were first detected in Wuhan, China in late December 2019. The first case of infection in Australia was confirmed on 25 January 2020 in an adult traveller from Wuhan.[1] Australia responded rapidly with an effective public health response: border controls were increasingly tightened until borders were effectively closed to all but returning residents by mid-March 2020, with mandatory 14-day quarantine for all arrivals. This was followed by bans on gatherings and non-essential travel, and most work occurring from home by April 2020.[2]

School closure was an early public health intervention implemented in many countries including Australia to prevent and control COVID-19 outbreaks. This was based on the knowledge that school closures are effective in pandemic and seasonal influenza response, where children drive transmission and outbreaks in schools are commonly observed.[3] However, analyses of the 2002–2003 SARS outbreak found that school transmission, in contrast to influenza, did not play a significant role in driving outbreaks in China, Hong Kong, or Singapore.[4] Additionally, available evidence early in the COVID-19 pandemic showed characteristics of SARS-CoV-2 in children may be different to those for influenza, particularly in children under 10 years of age,[5] with this group experiencing a lower burden of, and generally milder, disease than adults.[6-10] Likewise studies of household transmission indicated that younger children were unlikely to be primary cases in household clusters.[11-13] Furthermore, early modelling found that school closures were the least effective modelled intervention with little impact on projections and any benefits entirely offset by likely care arrangements in the home.[14]

On 17 March 2020, the Australian Health Protection Principal Committee issued recommendations on schools concluding that pre-emptive closure of schools would be a disproportionate intervention, with benefits overestimated and costs underestimated.[15] At this time, there had been a total of 375 confirmed cases nationally. However, on 23 March 2020, the New South Wales state government, with 869 total confirmed cases in the state, encouraged parents to keep children at home where possible[16] causing school attendance to drop to approximately 5% until mid-May.[17] Schools were remained open for children who needed to attend.

This study aimed to quantify and characterise transmission of SARS-CoV-2 in schools and early childhood education and care (ECEC) settings in order to inform public health policy regarding school closures and re-opening.

2.4 Methods

Study type

We conducted a prospective cohort study of secondary transmission among school- and ECEC-based close contacts of all notified laboratory-confirmed COVID-19 cases in students or teachers.

Study setting

All public, catholic and independent schools (n=3103) and ECECs (approx. n=4600) in NSW were eligible for inclusion where a confirmed COVID-19 case attended the school/ECEC while infectious from the beginning of the pandemic until 25 September 2020, which marked the end of school term three.

Case and close contact definitions

Confirmed and probable cases were defined using the definition in the COVID-19 Series of National Guidelines (SoNG) version 3.11 (Table 2.1).[18] A possible case was defined as anyone with detection of SARS-CoV-2 neutralising or IgG antibody AND who meets one or more of the epidemiological criteria defined in the SoNG.[18] This possible case definition is not in SoNG 3.11 and was included to capture asymptomatic cases diagnosed on convalescent serology only. A school or ECEC index case was defined as the first diagnosed confirmed case of COVID-19 in a school or ECEC. A school or ECEC primary case was defined as the confirmed COVID-19 case in that setting with the earliest infectious period. A close contact was defined as anyone with ≥15 minutes of face-to-face contact, or who shared a room with the case for a prolonged period of time (generally the same class) during the case's infectious period. This was more sensitive than the established definition for a close contact at the time, which defined a prolonged period of time as ≥2 hours. A secondary case was defined as any child or staff member who was likely to have acquired their infection due to an exposure at a school or ECEC. An external setting case was any case in the household or community linked to a school or ECEC case.

Table 2.1. Case definitions in the COVID-19 SoNG 3.11

Case type	Definition
Confirmed case	A person who: i. Tests positive to a validated NAT ii. Has the virus isolated in cell culture, with PCR confirmation using a validated method iii. Undergoes a seroconversion to or has a significant rise in SARS-CoV-2 neutralising or IgG antibody level (e.g. a four-fold or greater rise in titre)
Probable case	A person who has detection of SARS-CoV-2 neutralising or IgG antibody AND has had a compatible clinical illness AND meets one or more of the epidemiological criteria.
Suspect case	A person who meets the following clinical AND epidemiological criteria.
Clinical criteria	Fever (≥37.5°C) or history of fever (e.g. night sweats, chills) OR acute respiratory infection (e.g. cough, shortness of breath, sore throat) OR loss of smell or loss of taste.
Epidemiological criteria	In the 14 days prior to illness onset: • Close contact with a confirmed or probable case • International travel • Passengers or crew who have travelled on a cruise ship • Healthcare, aged or residential care workers and staff with direct patient contact • People who have lived in or travelled through a geographically localised area with elevated risk of community transmission, as defined by public health authorities

Routine public health and enhanced study follow up

All close contacts of a case received routine public health follow up from their Public Health Unit (PHU) or from the Public Health Emergency Operations Centre (PHEOC), including instructions to quarantine for 14 days following last exposure to the case, as well as daily or second daily mobile text message/phone call monitoring of symptoms. NCIMS records were made for each contact to facilitate this follow up. Initially in Term 1 and 2, contacts were instructed to present for COVID-19

testing if they developed COVID-19 symptoms. In Term 3, contacts were recommended to present for testing at day 3 and day 10 of their quarantine period regardless of symptoms.

In addition, we conducted enhanced investigations in selected schools/ECECs, consisting of: a) nasopharyngeal (NP) sample for SARS-CoV-2 nucleic acid test (NAT) between day 5 and day 10 following last exposure and irrespective of symptom presence (in Term 1 and 2 before testing recommendations were expanded), and b) blood collection for SARS-CoV-2 specific antibody testing (IgG, IgA, IgM) after 21 days following last exposure.

In Terms 1 and 2, schools included for enhanced surveillance were purposively selected based on feasibility in terms of location and timing, and with consent from the school leadership. Once routine testing rates increased in Term 3, enhanced surveillance consisting only of blood collection was performed in settings with delayed recognition of an outbreak where routine NAT testing occurred late. NP samples were collected from contacts either through a home visit from a medical team or through self-collection or collection by a parent/guardian facilitated by an instructional video and with telephone support from the study team where needed. Serology was offered regardless of whether the contact had previously undergone NAT and was collected either through a home visit by a medical team, at a central collection day at the school, or at a pathology centre.

Data collection and analyses

Data on laboratory testing results were obtained through NCIMS on a weekly basis. NCIMS was monitored until 28 days following last exposure to the case, after which a formal data extract for the cluster was downloaded and finalised for analysis.

Data on all COVID-19 notifications in NSW were obtained from the NSW Health website.[19]

Merging, cleaning, and analysis of these data was conducted using STATA version 14.2 (Statacorp LLC, College Station, TX, USA) and Microsoft Excel (Microsoft Corporation, 2010).

Laboratory testing

Ten public and three private laboratories carried out NAT for SARS-CoV-2 during the study period. Samples collected as part of enhanced surveillance were tested at the Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, using an in-house real-time polymerase chain reaction assay.[20] Serology for SARS-CoV-2 specific IgG, IgA, and IgM antibodies was performed using an immunofluorescence assay developed by ICPMR.[21]

Investigation of outbreaks

When secondary cases were identified in an educational setting, detailed case investigations were conducted to identify possible chains of transmission, and cases were mapped by their symptom onset and positive test dates.

Study oversight and ethics

This study was commissioned by the NSW Department of Health and conducted under the legislative authority of the NSW Public Health Act, 2010, with support from the NSW Department of Education.

2.5 Results

Primary cases and settings

Seventy-two primary cases were identified in 65 settings between 3 March and 25 September 2020 (Figure 2.1b), with seven schools having two co-primary cases (2.7 Appendix A). Introductions into schools coincided with periods of higher rates of community transmission (Figure 2.1a). Of the 65 settings, 28 (43.1%) were high schools (HS), 20 (30.8%) were primary schools (PS), and 17 (26.2%) were ECECs. There were 24 (33.3%) primary cases in staff, and 48 (66.7%) in students. The source of infection of primary cases was household contact in 34 (47%) cases, a non-household contact in 15 cases (21%), and unknown in 23 cases (32%).

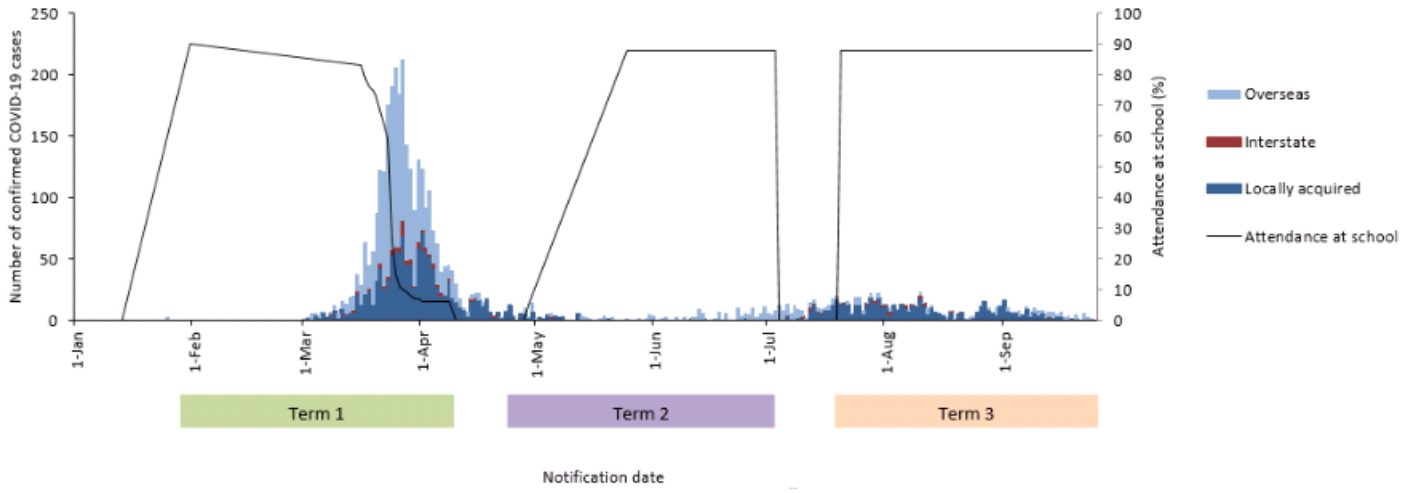


Figure 2.1a. Local, interstate (acquired in another jurisdiction), and overseas acquired cases and school attendance rates, New South Wales, 01 January to 25 September, 2020[19]

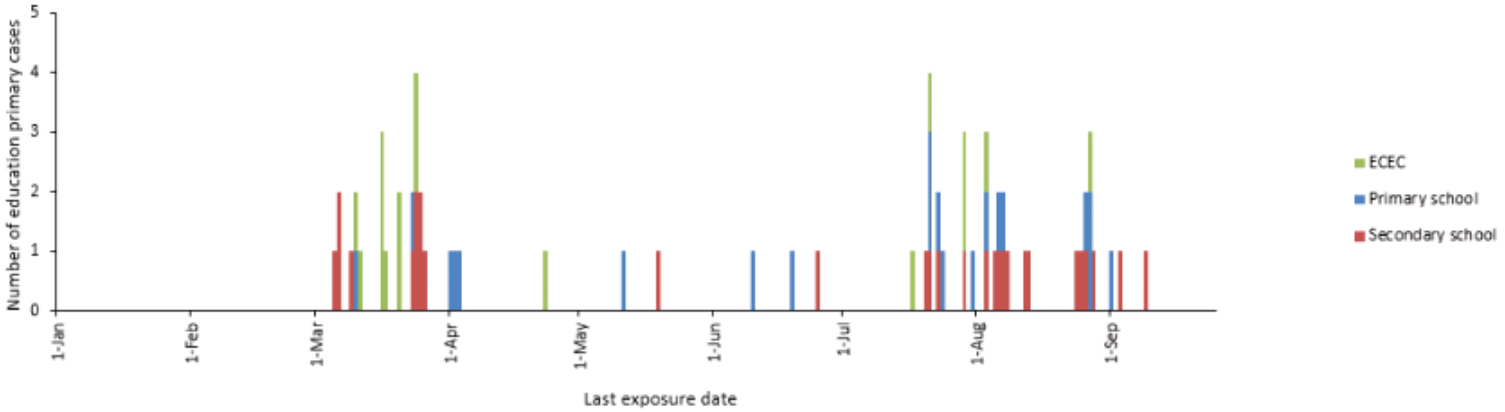


Figure 2.1b.Educational setting primary cases by date of last attendance at the educational facility, New South Wales, 01 January to 25 September, 2020

Contacts and testing

There were 5790 people identified as school or ECEC close contacts of these 72 primary cases: 5080 (87.7%) children and 710 (12.3%) staff. The median age of children across all settings was 12 (range <1–19 years) while the median age of staff was 38 (range 16–73 years) (2.7 Appendix A).

Of these 5790 contacts, 4607 (79.6%) contacts were tested by serology or NAT: 4062 (70.2%) contacts were tested by NAT only, 119 (2.1%) were tested by serology only, and 426 (7.4%) were tested by both serology and NAT. NAT rates increased from 43.7% (860/1969) in Term 1 and Term 2 to 95.0% (3628/3821) in Term 3.

Secondary cases

A total of 51 secondary cases (46 confirmed, one probable, and four possible) were identified across 14 (21.5%) settings, with the remaining 51 (78.5%) settings experiencing no secondary transmission (Table 2.2). The overall secondary attack rate in the study was 0.9% (51/5790). The majority of these cases (37/51; 72.5%) were from four high transmission settings that experienced ≥3 secondary cases. Of the 51 secondary cases, 38 (74.5%) were diagnosed based on NAT only, four (7.8%) were diagnosed based on serology only, and nine (17.6%) were positive based on both NAT and serology. Of the four diagnosed on serology only, two were mildly symptomatic children and were NAT-negative on day 4 and day 6 following last exposure, and two (one adult and one adolescent) were asymptomatic and did not undergo NAT.

Table 2.2. Details of primary cases, contacts, testing and secondary cases in 14 schools and ECECs with secondary SARS-CoV-2 transmission, New South Wales, 3 March–25 September 2020

Setting	Primary case/s age and sex	No. close contacts	Total tested by NAT or serology n(%)	Total secondary cases	SAR* (%)
HS01	14M,15F	211	154 (73.0)	1	0.5
HS02	13M, 15F	74	52 (70.3)	2	2.7
HS03	16F	292	290 (99.3)	14	4.8
HS04	17F	437	433 (99.1)	4	0.9
HS05	16M	226	225 (99.6)	6	2.7
HS06	13F	112	110 (98.2)	1	0.9
HS07	15M	127	127 (100)	2	1.6
PS01	46F	81	38 (46.9)	2	2.5
PS02	11M	247	204 (82.6)	1	0.4
PS03	70F	17	15 (88.2)	1	5.9
PS04	10F	56	56 (100)	1	1.8
ECEC01	49F	37	35 (94.6)	13	35.1
ECEC02	32F	88	86 (97.7)	1	1.2
ECEC03	57F	169	168 (99.4)	2	1.2

* SAR: secondary attack rate

High transmission outbreaks

Transmission in HS03

This outbreak was first recognised through a year 11 index case, case 2 (Figure 2.2) and the next day, another case (case 3) in a year 10 student was identified. The whole school were deemed contacts and the school was closed that day. An additional four cases were identified in students who had attended a two-night religious retreat with case 3. These five cases all shared a dormitory on the retreat. One of these students (case 4) was discovered to be a household contact of a confirmed case (case 1), who was identified while case 4 was on the retreat. Case 4 developed very mild symptoms and tested positive on day 10, but it is likely that she had an earlier asymptomatic infection and was infectious before and during the retreat.

After returning from the retreat, case 3 performed in a contemporary music group in the school hall on day 5. Sixteen students and one teacher were in attendance. Of these 17 people, six additional people become cases.

Two days after the music class, a study group was held at the same location as the retreat. Case 3 attended this study group with a number of students across year groups. Two students from her year group became cases, however these people also attended the music group (case 5 and case 22). An additional case was diagnosed in a student from a different year group (case 11), but this case was in a different room throughout the study group and no clear contact could be traced between case 11 and the other cases. In addition to these events, students also had contact during normal school hours in the week before the school was closed. Cases 2, 21, and 16 may have been exposed during normal school activities.

Transmission in HS04

This outbreak was recognised when two students (case 1 and case 2) in two different year groups tested positive within a day of each other after each attending school while symptomatic for a week (Figure 2.3). As these two cases had no contact with each other and neither had a clear source of infection, the whole school was instructed to quarantine and undergo testing. Case 9 and her brother, case 10, were both asymptomatic and returned negative NATs but had serology performed because their parents were confirmed cases. The serology was positive and placed their infections around day 1 of the outbreak. Case 1 was likely case 3's source of infection, as she sat next to case 1 in class. Case 3 and case 5 are siblings. The expansion of testing to the whole school revealed no additional cases. This was a large high school with a small campus, making distancing of students difficult. Additionally, the school had mixed-grade homerooms, resulting in mixing of students across year groups.

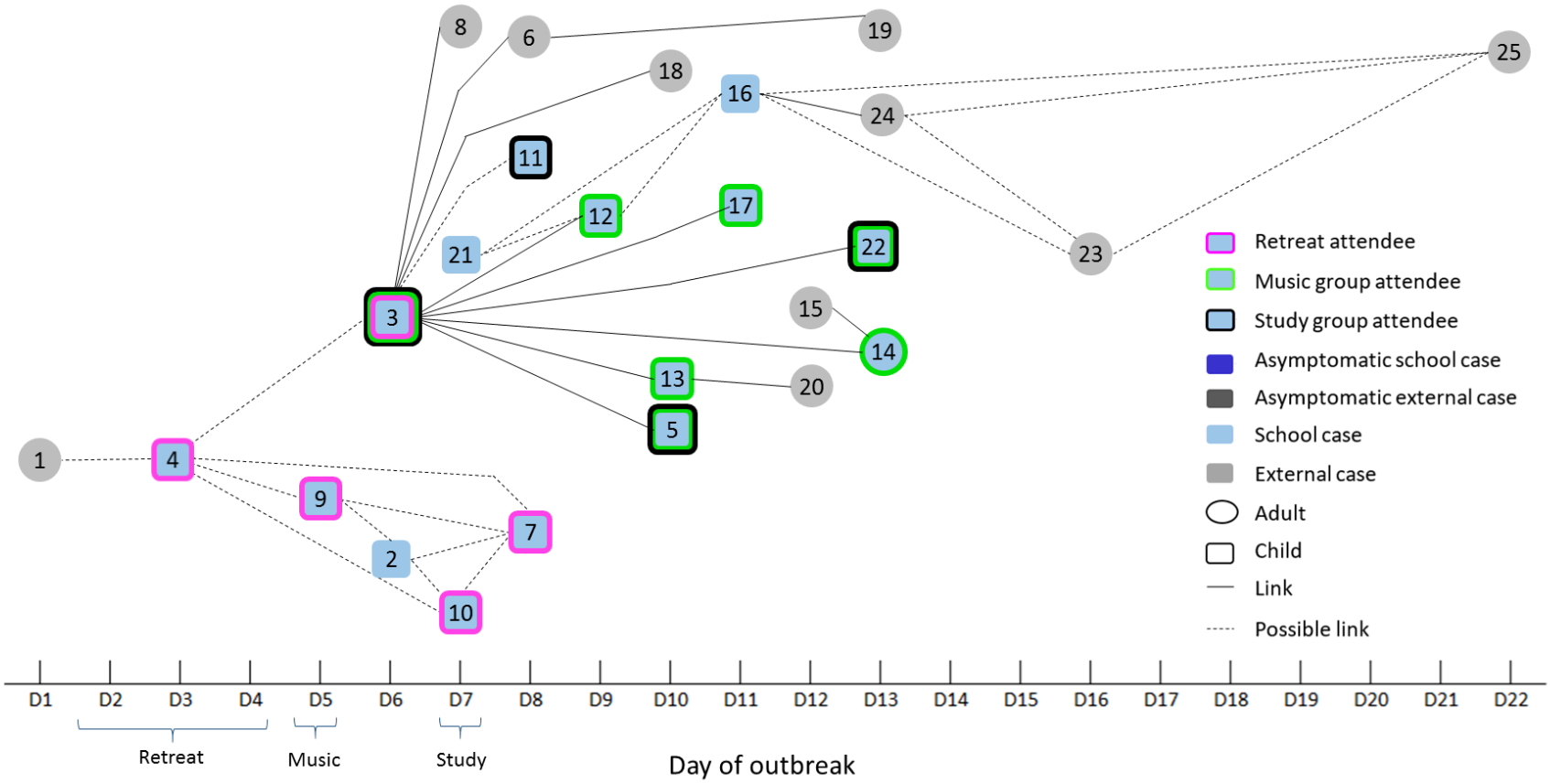


Figure 2.2. Likely and possible chains of transmission between COVID-19 cases in HS03, New South Wales, 2020

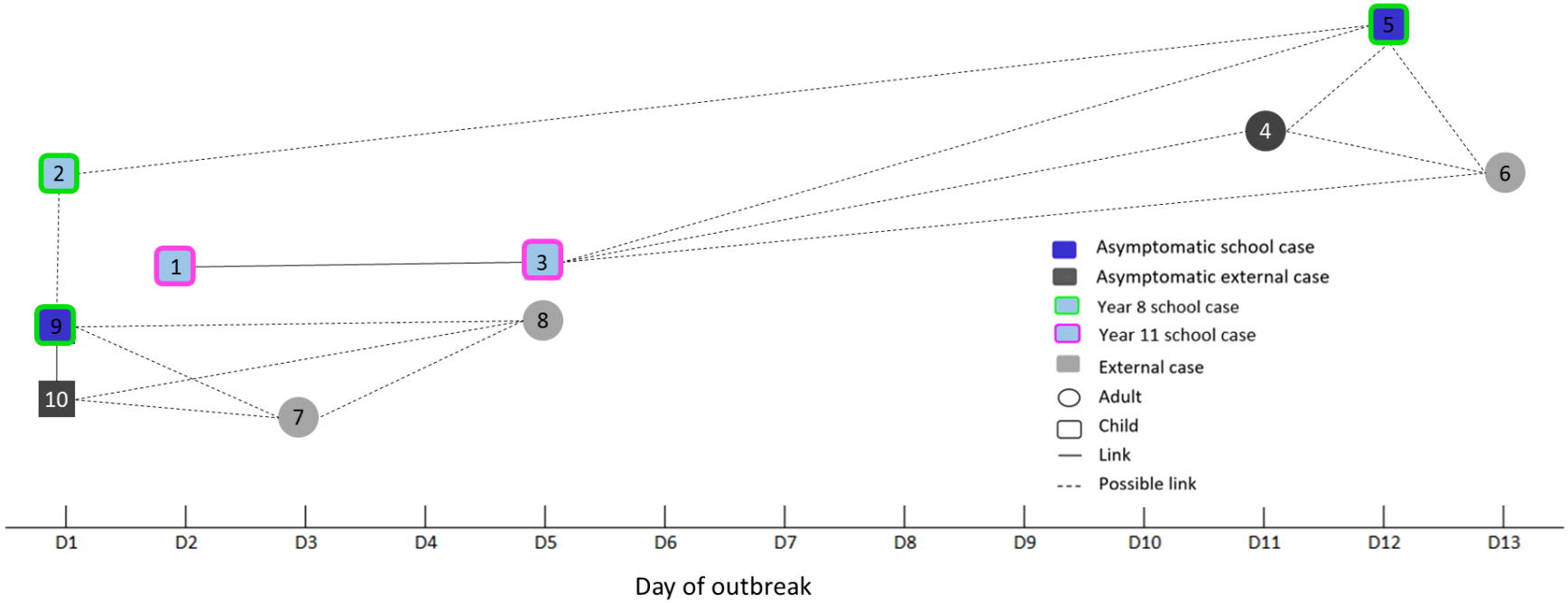


Figure 2.3. Likely and possible chains of transmission between COVID-19 cases in HS04, New South Wales, 2020

Transmission in HS05

This outbreak was detected through case 1, who had an unknown source (Figure 2.4). Case 1 attended school for three days while symptomatic and infectious. Six secondary cases were diagnosed. Case 2 also attended for three days following symptom onset. All six secondary cases shared between two and five classes with case 1, and between five and nine classes with each other. Case 5 tested positive at the same time as his household contacts, cases 6 and 7, who had no known additional exposures. Case 5 was asymptomatic at the time of testing positive but went on to develop mild symptoms.

Transmission in ECEC01

This cluster was first recognised through the diagnosis of disease in a toddler (case 1), who attended an ECEC that catered for children from <1–5 years, split across a babies room, toddler room, and pre-school room. However, public health follow up of the case revealed a number of staff with an earlier illness who had contact with case 1 in the babies room, and case 2 was later identified to be the primary case of the cluster. Case 2 worked for one day while pre-symptomatically infectious, during which time she cared for case 1 (Figure 2.5).

This is a small ECEC, with sharing of kitchen facilities and one bathroom. Further contact tracing resulted in diagnosis of a further four cases in staff (cases 13–16), some of whom had not had exposure in the babies room, and the decision was made to close the centre and expand public health follow up to the entire ECEC.

A number of these staff presented for testing at the time of symptom onset, but were denied as the testing criteria at the time required either recent international travel or contact with a confirmed case. The staff didn't meet these criteria until case 1 was diagnosed outside of the criteria at a children's hospital. The PHU was notified of the index case (case 1) nine days after symptom onset of the primary case (case 2), by which time two generations of transmission had occurred.

In total 13 cases (12 confirmed and one probable) in seven children and six adults were diagnosed in ECEC attendees, and an additional 15 cases in household or community contacts of these cases. Parents of case 1 and case 23 became cases, but these parents also had direct contact with ECEC staff during pickup and drop-off. Three of the children were asymptomatic and were tested outside of public health recommendations as part of enhanced investigations.

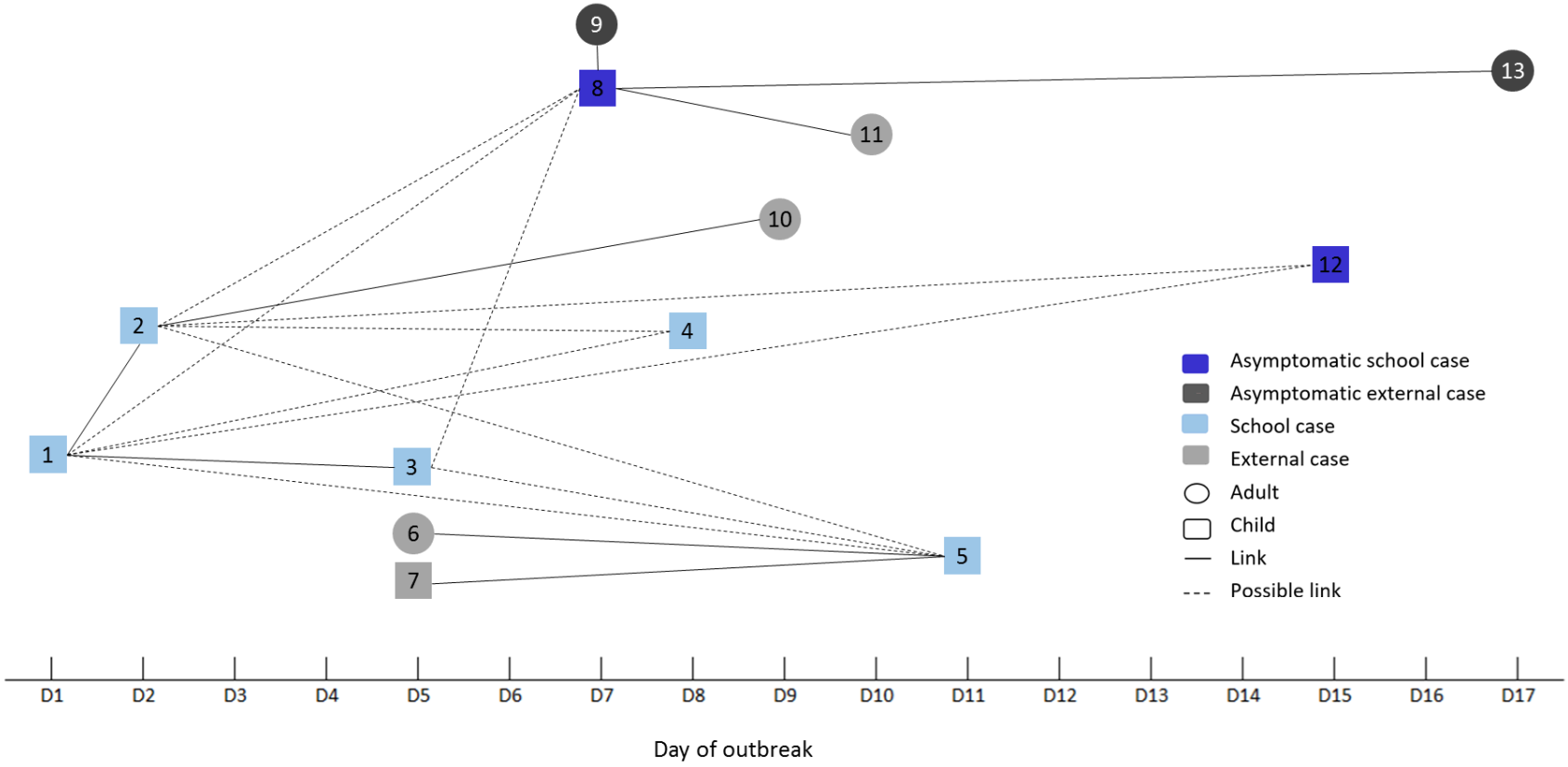


Figure 2.4. Likely and possible chains of transmission between COVID-19 cases in HS05, New South Wales, 2020

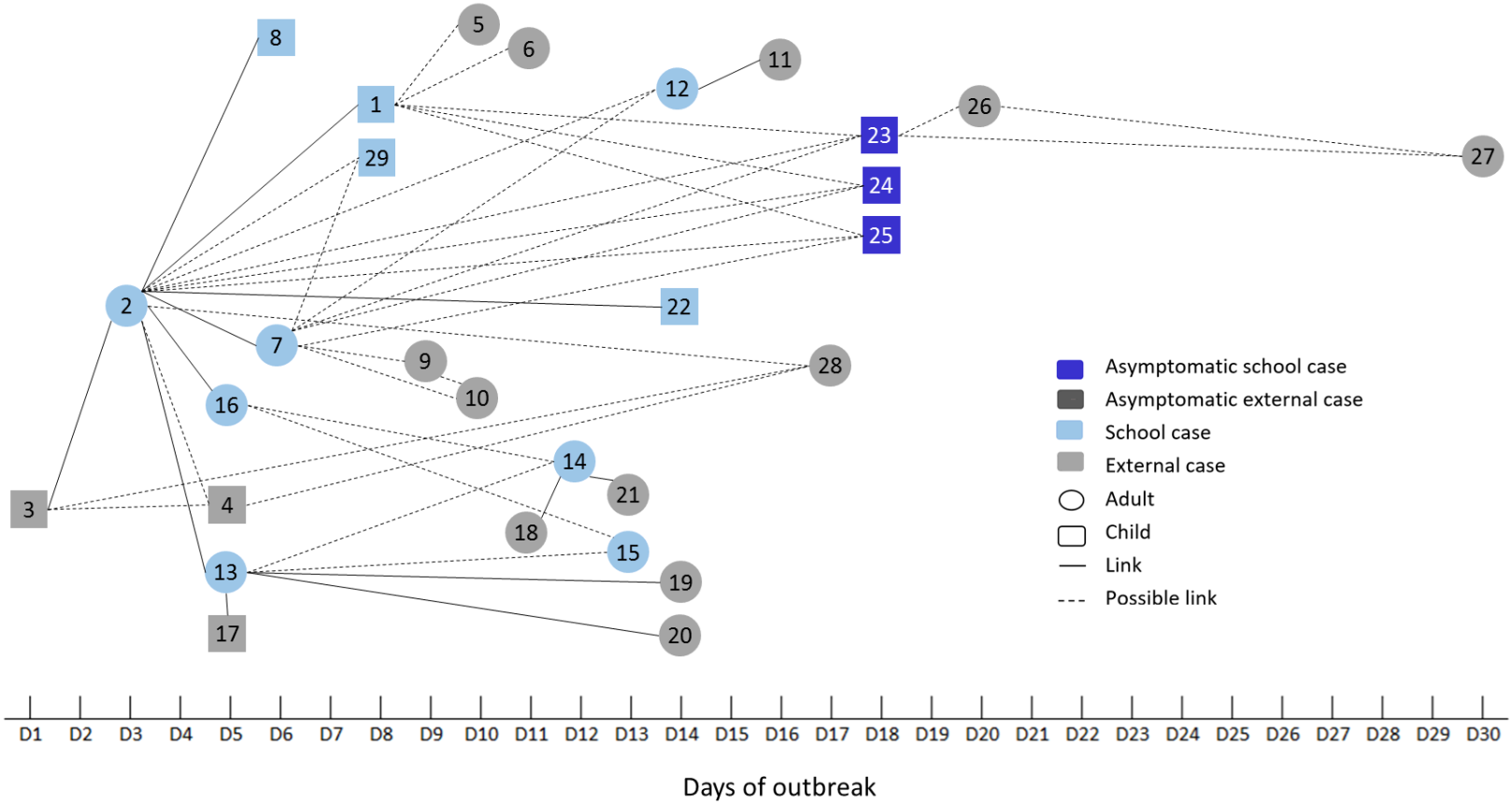


Figure 2.5. Likely and possible chains of transmission between COVID-19 cases in ECEC01, New South Wales, 2020

2.6 Discussion

This study shows limited but variable transmission of SARS-CoV-2 in educational settings. Primary cases did not transmit within the educational setting in 78.5% of introductions, and where transmission did occur, outbreaks were limited to 1–2 secondary cases in 71.4% of settings. Among the settings with more substantial transmission (≥ 3 secondary cases), delayed testing and outbreak recognition, mixing of students and staff, prolonged and very close contact or household-like settings, and specific high risk events likely contributed to onward spread. Together, our data are consistent with emerging international evidence of low transmission in educational settings[22-32]. The results of this study must be interpreted within the context of the 2020 NSW outbreak. The low transmission rates reported in this study are likely to have been underpinned by a strong public health response. All cases and contacts were effectively traced and isolated, and schools and ECECs were temporarily closed following detection of a case to enable deep cleaning, therefore creating fewer transmission opportunities within the educational setting. This study also occurred at a time before variants of concern were circulating in Australia and findings may be not be applicable to variants with different transmission dynamics.

Transmission within four settings accounted for 72.5% of cases acquired in an educational setting to 25 September 2020. An emerging feature of the COVID-19 pandemic is overdispersion, where a small proportion of cases are responsible for the majority of spread.[33-35] The possible reasons for overdispersion relate to biological, behavioural, and opportunistic mechanisms, including differences in viral shedding, the environment, population density and susceptibility, and social contact behaviours.[33-35]

The secondary attack rates in the high-transmission high schools are likely to be artificially low, as a more sensitive close contact definition was used in high-transmission settings, often including the whole year group or school. The observation that three of these high transmission settings were high schools, and high schools accounted for 50% (7/14) of settings with any transmission, is in line with studies conducted in other countries, suggesting that SARS-CoV-2 spreads among adolescents more efficiently than younger children.[26, 36, 37] Additionally, the fourth high-transmission setting was an ECEC, but transmission in this setting appeared to be driven by adult staff. Evidence is emerging that children may become infected with SARS-CoV-2, but may be less likely to transmit, possibly due to age-related immunological differences.[38, 39]

The delay in testing and subsequent delay in recognition of the outbreak in ECEC01 resulted in two generations of transmission occurring before public health interventions could be enacted. This

delay was due to the narrow testing criteria early in the pandemic,[40] and may highlight the need to have more flexible testing criteria for clearly symptomatic people early in pandemic response when transmission characteristics are not clear.

Similarly, four cases across HS04 and HS05 attended school for 3–5 days while symptomatic before being tested, resulting in prolonged contact hours between cases and contacts. This highlights the need for stay-at-home-if-sick messaging, which is part of a suite of school-based mitigation measures that may reduce the risk of transmission.[41] However, of the 51 secondary cases identified in this study, 10 (19.6%) remained asymptomatic, including three infants, five adolescents, and two adults. This is consistent with existing research indicating high rates of asymptomatic infection with SARS-CoV-2 infection, especially in children.[6, 8-10, 42] Asymptomatic cases may contribute to delayed outbreak recognition, as in HS04, which may have been seeded by asymptomatic cases. Notably, the known symptom profile of COVID-19 evolved as more was learnt about the disease, and it's possible that some of these cases may not have been truly asymptomatic.

There was also increased mixing in HS04 due to mixed grade homerooms and a relatively small campus with a large number of students, increasing transmission possibilities. Interventions aimed at reducing congregation of large groups of people who would otherwise rarely meet is likely to have an outsized effect on control in outbreaks where overdispersion is a feature.[34] As such, reducing mixing of students and staff within schools may reduce the risk of transmission. This may be achieved by avoiding mixed grade classes, staggering staff breaks, and reducing the use of staff common areas.

Along with increased mixing, very close contact was common among high-transmission settings in our study. The small size of the centre and the closeness of interactions between attendees in ECEC01 meant the transmission dynamics within the ECEC were more akin to household transmission. SARS-CoV-2 is known to spread efficiently in household settings.[12] Similarly, there was crowding of students in HS04 due to the small campus. The high secondary attack rate reported in a large outbreak in a high school in Israel was attributed to a heatwave involving continuous air-conditioning use and crowded classrooms.[43] Physical distancing where able may reduce the risk of transmission.

The retreat in HS03 was a high-risk event driven by students sharing a dormitory, also making transmission in this setting household-like. An outbreak with a high secondary attack rate has been reported in an overnight camp in the United States of America,[44] suggesting this is a high-risk activity. Similarly, six of the secondary cases in the HS03 were likely infected during music class: a

second high-risk event in the cluster. Group singing and wind instruments have been implicated in a number of outbreaks, including one of high transmission.[45, 46] The risk of outbreaks may be reduced by limiting higher risk activities, such as singing and wind instruments, and school camps, to times when community incidence of disease is low.

This study has several limitations. Incomplete testing of contacts earlier in the study period may have meant that asymptomatic cases or those with mild symptoms were missed, particularly in settings in which enhanced investigations were not carried out. However, testing rates were 95% in Term 3, and results were consistent with those from earlier in the year. Reporting of symptom onset may have been affected by recall bias, difficulty in recognising mild symptoms, or hesitancy about reporting continued attendance while symptomatic, particularly in settings that received significant media attention. This may have affected described transmission directions, and may explain negative or short serial intervals between cases.

Our findings suggest that effective outbreak control can be accomplished with schools remaining open in the context of a strong public health response and low community incidence of disease. However, outbreaks can occur in schools, and risk may be reduced through physical distancing, reducing mixing of students, reducing the use of staff common areas and staggering staff breaks, encouraging staff and children to stay home if unwell, and limiting higher risk activities to periods of low community incidence of disease.

2.7 Appendices

Appendix A. Primary COVID-19 cases, close contacts and secondary cases who attended 65 educational settings from 3 March to 25 September, New South Wales, 2020

Term	No. settings	No. Student primary cases	No. Staff primary cases	Student contacts								Staff contacts							
				No.	Age median (range)	NAT		Serology		Total		No.	Age median (range)	NAT		Serology		Total	
						N (%) NAT tested	N (%) NAT positive	N (%) serology tested	N (%) serology positive	N (%) total tested	N total positive (SAR%)*			N (%) NAT tested	N (%) NAT positive	N (%) serology tested	N (%) serology positive	N (%) total tested	N total positive (SAR%)*
High school																			
Term 1	10	8	4	600	15 (11–19)	196 (32.7%)	0	123 (20.5%)	2 (1.6%)	**253 (42.2%)**	**2 (0.3%)**	96	44 (21–73)	39 (40.6%)	0	11 (11.5%)	1 (9.1%)	**44 (45.8%)**	**1 (1.0%)**
Term 2	2	2	0	164	12 (12–17)	86 (52.4%)	0	0	0	**86 (52.4%)**	**0**	23	36 (23–70)	17 (73.9%)	0	0	0	**17 (73.9%)**	**0**
Term 3	16	19	1	2289	15 (11–18)	2229 (97.4%)	26 (1.2%)	188 (8.2%)	1 (0.5%)	**2235 (97.6%)**	**26 (1.1%)**	235	43 (20-69)	232 (98.7%)	1 (0.4%)	27 (11.5%)	0	**232 (98.7%)**	**1 (0.4%)**
Total	**28**	**29**	**5**	**3053**	**15 (11–19)**	**2511 (82.2%)**	**26 (1.0%)**	**311 (10.2%)**	**3 (1.0%)**	**2574 (84.3%)**	**28 (0.9%)**	**354**	**42.5 (20–73)**	**288 (81.4%)**	**1 (0.3%)**	**38 (10.7%)**	**1 (2.6%)**	**293 (82.8%)**	**2 (0.6%)**
Primary school																			
Term 1	5	1	4	179	9 (4–11)	42 (23.5%)	1 (2.4%)	31 (17.3%)	1 (3.2%)	**55 (30.7%)**	**1 (0.6%)**	39	36 (19–64)	20 (51.3%)	1 (5.0%)	7 (17.9%)	0	**23 (59.0%)**	**1 (2.6%)**
Term 2	3	1	2	211	7 (4–12)	111 (52.6%)	0	34 (16.1%)	0	**129 (61.1%)**	**0**	21	29 (21–58)	21 (100%)	0	4 (19.0%)	0	**21 (100%)**	**0**
Term 3	12	11	2	779	9 (4–12)	668 (85.8%)	2 (0.3%)	51 (6.5%)	0	**671 (86.1%)**	**2 (0.3%)**	80	39 (21–71)	79 (98.8%)	1 (1.3%)	12 (15.0%)	0	**80 (100%)**	**1 (1.3%)**
Total	**20**	**13**	**8**	**1169**	**8 (4–12)**	**821 (70.2%)**	**3 (0.4%)**	**116 (9.9%)**	**1 (0.9%)**	**855 (73.1%)**	**3 (0.3%)**	**140**	**36.5 (19–71)**	**120 (85.7%)**	**2 (1.7%)**	**23 (16.4%)**	**0**	**124 (88.6%)**	**2 (1.4%)**
ECEC																			
Term 1	10	3	7	406	3 (<1–5)	182 (44.8%)	6 (3.3%)	36 (8.9%)	5 (13.9%)	**194 (47.8%)**	**7 (1.7%)**	128	33 (16–73)	63 (49.2%)	6 (9.5%)	9 (7.0%)	2 (22.2%)	**64 (50.0%)**	**6 (4.7%)**
Term 2	1	1	0	84	4 (<1–10)	68 (81.0%)	0	6 (7.1%)	0	**68 (81.0%)**	**0**	18	32 (22–54)	15 (83.3%)	0	0	0	**15 (83.3%)**	**0**
Term 3	6	2	4	368	3 (<1–5)	352 (95.7%)	0	6 (1.6%)	0	**352 (95.7%)**	**0**	70	30 (18–70)	68 (97.1%)	3 (4.4%)	0	0	**68 (97.1%)**	**3 (4.3%)**
Total	**17**	**6**	**11**	**858**	**3 (<1–10)**	**602 (70.2%)**	**6 (1.0%)**	**48 (5.6%)**	**5 (10.4%)**	**614 (71.6%)**	**7 (0.8%)**	**216**	**32 (16–73)**	**146 (67.6%)**	**9 (6.2%)**	**9 (4.2%)**	**2 (22.2%)**	**147 (68.1%)**	**9 (4.2%)**
All settings																			
Term 1	25	12	15	1185	10 (<1–19)	420 (35.4%)	7 (1.7%)	190 (16.0%)	8 (4.2%)	**502 (42.4%)**	**10 (0.8%)**	263	37 (16–73)	122 (46.4%)	7 (5.7%)	27 (10.3%)	3 (11.1%)	**131 (49.8%)**	**8 (3.0%)**
Term 2	6	4	2	459	8 (<1–17)	265 (57.7%)	0	40 (8.7%)	0	**283 (61.7%)**	**0**	62	31.5 (21–70)	53 (85.5%)	0	4 (6.5%)	0	**53 (85.5%)**	**0**
Term 3	34	32	7	3436	13 (<1–18)	3249 (94.6%)	28 (0.9%)	245 (7.1%)	1 (0.4%)	**3258 (94.8%)**	**28 (0.8%)**	385	39 (18–71)	379 (98.4%)	5 (1.3%)	39 (10.1%)	0	**380 (98.7%)**	**5 (1.3%)**
Total	**65**	**48**	**24**	**5080**	**12 (<1–19)**	**3934 (77.4%)**	**35 (0.9%)**	**475 (9.4%)**	**9 (1.9%)**	**4043 (79.6%)**	**38 (0.7%)**	**710**	**38 (16–73)**	**554 (78.0%)**	**12 (2.2%)**	**70 (9.9%)**	**3 (4.3%)**	**564 (79.4%)**	**13 (1.8%)**

* SAR= Secondary attack rate out of total contacts

Appendix B. Public summary of Term 3 School Study results

COVID-19 in schools and early childhood education and care services – the Term 3 experience in NSW

Prepared by the National Centre for Immunisation Research and Surveillance (NCIRS)
21 October 2020

Overview

- This report provides an overview of investigation into all COVID-19 cases in the state of New South Wales (NSW), Australia in all schools and early childhood education and care (ECEC) services between 4 July 2020 and 25 September 2020 (school term 3 of the academic year).
- 39 individuals (32 students and 7 staff members) from 34 educational settings (28 schools and 6 ECEC services) were confirmed as primary COVID-19 cases who had an opportunity to transmit the SARS-CoV-2 virus to others in their school or ECEC service.
- 3,824 individuals (3,439 students [90%] and 385 [10%] staff members) were identified as close contacts of these 39 primary cases.
- 33 secondary cases (28 students and 5 staff members) occurred in 10 educational settings (5 high schools, 3 primary schools, 2 ECEC services).
- For details on Term 1 and Term 2 data, refer to NCIRS report here or view our publication in The Lancet Child and Adolescent Health here.

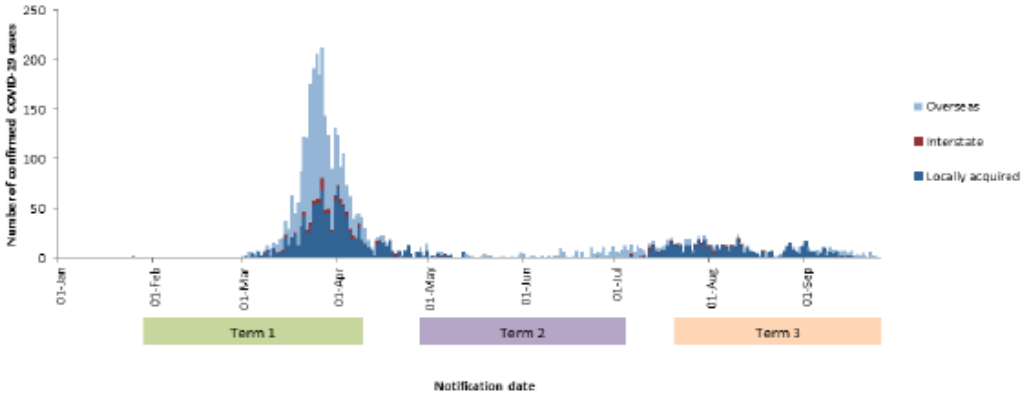
Background

The National Centre for Immunisation Research and Surveillance (NCIRS), with the support of the NSW Ministry of Health and NSW Department of Education, has been conducting surveillance of SARS-CoV-2 transmission in educational settings throughout the 2020 school year in New South Wales, Australia (state population 8.1 million). School term 1 (28 January to 9 April 2020) coincided with the start of the COVID-19 pandemic and the first wave in NSW. During term 2 (27 April to 3 July 2020), there was minimal community transmission of COVID-19.

From 6 July 2020 just prior to Term 3 commencement, there was an increase in locally acquired COVID-19 cases in NSW, initiated by interstate travellers from the adjacent state of Victoria which was experiencing a large outbreak[1] (refer to Figure 1).

In Term 3 (4 July to 25 September 2020), there were 774 cases across NSW, with 555 cases locally acquired of which 106 (19%) were aged <18 years. Schools remained open for face-to-face learning, while implementing COVID-19 safe practices (refer to Appendix), and recorded high attendance rates (88%). ECEC services also remained open throughout the winter school holidays and all of Term 3.

Figure 1: COVID-19 cases by likely infection source and notification date, NSW 2020[2]



Methods

Laboratory-confirmed paediatric (aged ≤18 years) and adult COVID-19 cases who attended a school or ECEC service while considered infectious (defined as 24 hours before symptom onset, based on national guidelines during the study period) were investigated for onward transmission.

Full details of our methods can be found in previous reports and in our publication.[3]

A 'close contact' is defined as a person who has been in face-to-face contact for at least 15 minutes or in the same room for 2 hours with a case while infectious (i.e. during their symptomatic period and 48 hours before symptom onset). Because physical distancing has not been implemented among students in schools and ECEC services, the inclusion criteria for being a close contact were broadened to include any person who was in the same room for 1 hour or more with a case while infectious.

An outbreak is defined as ≥2 secondary cases in a school or ECEC service.

Results

In Term 3, 34 educational settings (16 high schools, 12 primary schools and 6 ECEC services) were investigated for having a case with COVID-19 in staff member or student who attended while infectious.

There were 39 primary COVID-19 cases (32 students and 7 staff members; Figure 2), all of whom acquired infection via local transmission. The majority of cases (22 students and 3 staff members; 64%) acquired COVID-19 through household contacts, followed by community non-household contacts (6 students and 3 staff members; 23%) and five cases (13%) had no known contact source and had not travelled (4 students and 1 staff member).

Public health staff identified 3,824 close contacts of the 39 primary cases (3,439 students and 385 staff members), of whom 3,641 (95.2%) contacts were tested: nose/throat swabs for nucleic acid testing (NAT) were taken from 3,631 (95.0%) of contacts and antibody testing was performed on 278 (7.3%) contacts.

Thirty-three secondary cases (28 students and 5 staff members) occurred in 10 settings (5 high schools, 3 primary schools, 2 ECEC services), with an overall secondary attack rate of 0.9% (33/3,641). All students and staff cases had mild infection and did not require hospitalisation.

High schools

A total of 20 COVID-19 primary cases (19 students and 1 staff member) who attended 16 high schools while infectious were identified. Three schools had co-primary cases (siblings) and one school had two separate clusters (2 separate student index cases).

The total number of close contacts in these 16 high schools was 2,526 (2,291 students and 235 staff members). Of these, 2,466 (97.6%) contacts were tested: nose/throat swabs for NAT were taken from 2,460 (97.4%) of contacts and antibody testing was performed on 211 (8.4%) contacts. Of these 2,466 contacts, 27 tested positive (26 students and 1 staff member) in five schools, as shown in Figure 3.

Outbreaks were identified in four high schools. The secondary attack rate in high schools was 1.1% (27/2,466).

High school outbreak 1	**High school outbreak 2**
The index case (first identified case) was a student whose source of infection was unknown. Contact tracing and testing revealed a further four cases in students. Of these, one tested positive on antibody testing and may have been the primary case and one was a sibling who likely acquired the infection within the household.	The index case was a student. Contact tracing and testing revealed further 14 cases (13 students and 1 staff member). One student was a previous close contact of a household member and may have been the primary case. Transmission occurred during an out of school retreat and in a school music group.
High school outbreak 3	**High school outbreak 4**
The primary case was a student whose source of infection is unknown. Contact tracing and testing revealed further six cases in students.	The primary case was a student who acquired infection via household transmission. There were further two cases (in siblings) identified within the school.

Primary schools

A total of 13 primary cases (11 students and 2 staff members) were identified in 12 primary schools. One school had co-primary cases (siblings).

The total number of close contacts in these primary schools was 859 (779 students and 80 staff members). Of these, 754 (87.8%) contacts were tested: nose/throat swabs for NAT were taken from 750 (87.3%) of contacts and antibody testing was performed on 64 (7.5%) contacts.

There were no outbreaks within the primary school setting. Overall, as shown in Figure 4, three individuals (2 students and 1 staff member) in three schools were identified as infected following close contact with a school case. SARS-CoV-2 antibodies were not detected in any of the 64 contacts.

ECEC services

Six primary cases (2 children and 4 staff members) were identified in six ECEC services.

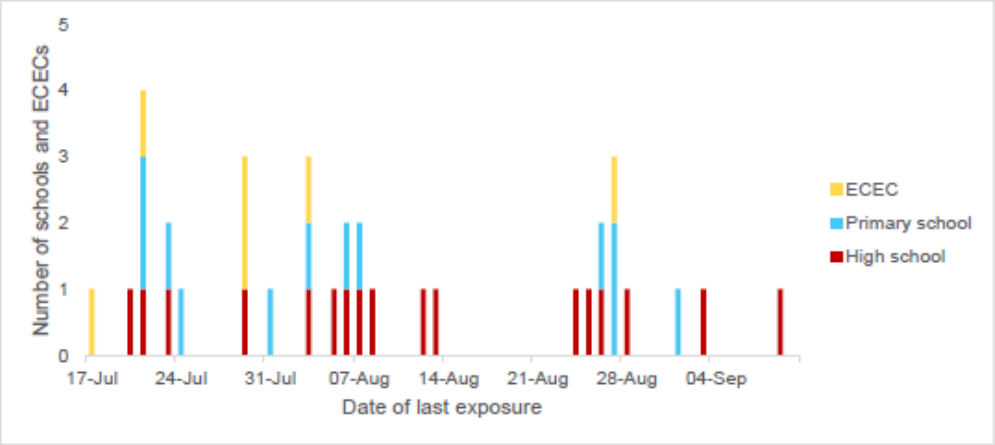
The total number of close contacts was 439 (369 children and 70 staff members). Of these, 421 (95.9%) contacts were tested: nose/throat swabs for NAT were taken from 421 (95.9%) of contacts and antibody testing was performed on 3 (0.7%) contacts.

Overall, as shown in Figure 5, three individuals, all staff members, were infected following close contact with an ECEC case. An outbreak occurred in one setting.

ECEC service outbreak

The primary case (staff member) acquired infection via household transmission. Contact tracing and testing revealed two secondary cases in staff members.

Figure 2: NSW schools and ECEC services with a COVID-19 primary case(s) in Term 3*



*One high school had 2 separate unrelated primary cases.

Figure 3: Cases and close contacts among staff members and students in 16 NSW high schools in Term 3

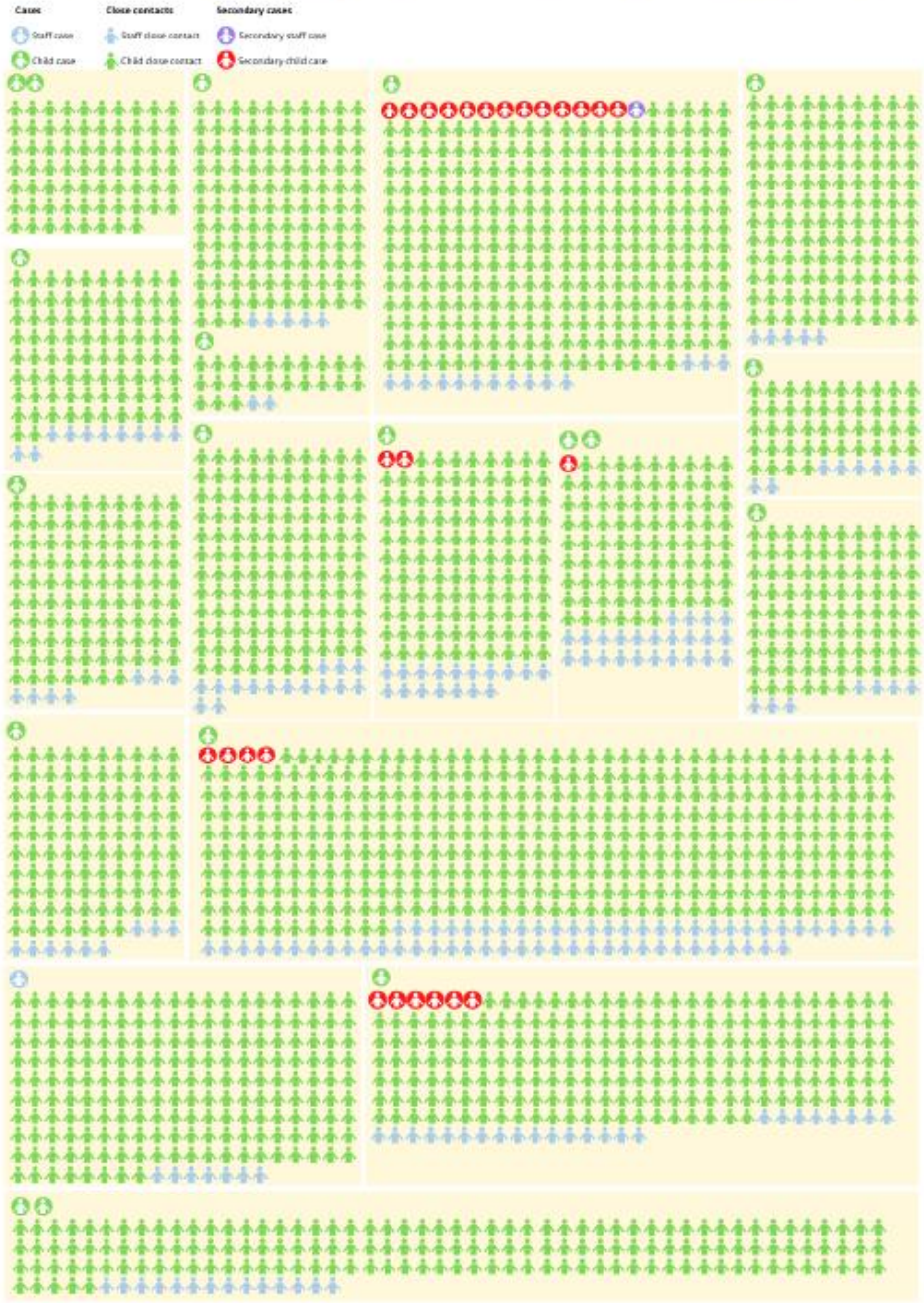
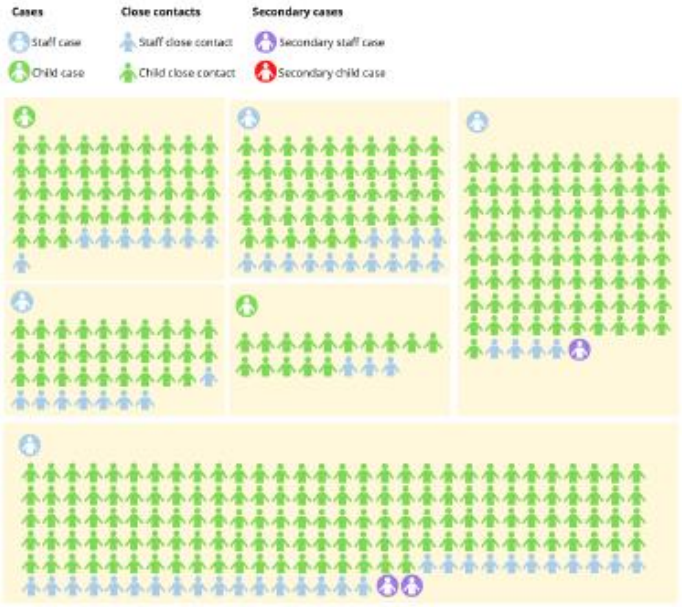


Figure 4: Cases and close contacts among staff members and students in 12 NSW primary schools in Term 3

Figure 5: Cases and close contacts among staff and children in 6 NSW ECEC services in Term 3



Excluded cases/settings

One primary school had a staff member who had a false positive nucleic acid test for SARS-CoV-2 on a throat swab. A public health response occurred (closure and cleaning of school, contact tracing and self-isolation of close contacts). All 29 close contacts (100%) underwent NAT and returned negative result.

Repeat NAT and antibody testing on the case were also negative. As a result, the staff member and all their close contacts returned to school before the end of the isolation period.

Conclusion

In July 2020, NSW experienced a rise in COVID-19 cases, stemming from imported interstate cases and several cascading chains of transmission. Between 4 July and 25 September, rate of infection in NSW was 10 per 100,000 population.[2] Local community transmission was responsible for the majority of cases (71%) in Term 3, compared with Term 1 (37%). Implementation of COVID-19 safe practices, including limiting parents and visitors onsite, increased cleaning and hygiene measures and other measures (refer to Appendix) continued into Term 3. Schools and ECEC services remained open with high attendance rates (88%).

The overall secondary transmission rate was 0.9% (33/3,641) for all settings: 1.1% in high schools, 0.4% in primary schools and 0.7% in ECEC services. The highest rate of transmission in primary schools and ECEC services was among adults, at 6.6%.

Three larger outbreaks occurred, all in high school settings. Factors that may have contributed to these outbreaks include attending school while symptomatic, a non–school-related overnight retreat and participation in a music group. All outbreaks were rapidly contained with NSW public health response strategy.

The likelihood of cases in educational settings is related to the level of community transmission of SARS-CoV-2. This is consistent with findings from Victoria, Australia[4] and from international studies.[5–7]

Data from Term 3 in NSW show that even with increased rate of testing (>95%), and consistent with our previous reports and publication, secondary transmission within schools and ECEC services was low. We found that the overall rate of transmission was the lowest in primary schools and there was no transmission among children in ECEC services. This is consistent with other evidence that shows younger children appear less likely than adults to transmit SARS-CoV-2.[8–12]

Closure of schools has a direct impact on learning, increasing educational disparities and exposing children to vulnerabilities at home.[13–14] The key to keeping schools and ECEC services open and maintaining face-to-face learning in NSW has been compliance with COVID-19 safe practices, flexibility to implement and ease restrictions on activities (especially those that carry increased risk of transmission such as music groups, overnight stays, parent gatherings) depending on rates of infection in the community, widespread access to SARS-CoV-2 testing and a comprehensive coordinated public health strategy of contact tracing and isolation that has resulted in low rates of community transmission.

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Chapter 3

Australian Vaccine Preventable Review Series: measles, 2012–2019

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3.1 Prologue

Background

Under its funding agreement with the Commonwealth Department of Health, NCIRS produces reports as part of a series titled the Australian Vaccine Preventable Disease Epidemiological Review Series. Measles was chosen as the topic for the 2021 report. This Chapter also contains a literature review on the effect of the COVID-19 pandemic on measles vaccination coverage in the South East Asia and Western Pacific regions.

My role

My role for this project was as the principal investigator. I planned the study, submitted the ethics application, requested the data, cleaned and analysed the data, and was the lead author on the resulting manuscript. I was also the corresponding author for the submission to *Communicable Diseases Intelligence*.

Public health impact

Australia was verified as having eliminated measles in 2014. However, in that same year, Australia recorded a 16 year high in measles notifications on the background of a global surge in cases that has seen global progress towards elimination stall. This resurgence is set to worsen, as the COVID-19 pandemic has interrupted routine and mass vaccination efforts overseas, exacerbating immunity gaps. This study is the first detailed review of Australian measles epidemiology in the elimination era. It will inform future immunisation policy and serve as a baseline for monitoring imported cases when Australia's international borders reopen.

This manuscript was submitted to the Department of Health as a contract deliverable and was submitted for publication in *Communicable Diseases Intelligence.*

Lessons learnt

This was the first project in which I used STATA to clean data. Once I had lines of code that worked, Dr Quinn showed me more elegant ways of achieving the same results using loops. I also became practiced at poring over historical coverage surveys and the long histories of measles vaccination campaigns and schedules in Australia in order to create birth cohorts of cases with a likely similar vaccination history and levels of immunity. I learnt about epidemiological aspects of measles, such as expected trends in genotypic diversity as countries and regions progress towards elimination of

measles. In addition to these, I learnt to apply some principles of scientific writing, such as structuring of the Discussion, and the correct use of voice and tense, with guidance from Dr Beard. I also learnt to be precise in not over-interpreting or under-interpreting data.

I also learnt about systematic literature search techniques, including the uses of Medical Subject Heading (MeSH) terms and adjacency operators.

Acknowledgements

I would like to acknowledge Dr Dey, Dr Quinn, and Dr Pourmarzi for their feedback and comments on the Chapter. I would especially like to thank Dr Beard for his valuable time in reviewing multiple iterations of drafts with detailed feedback, A/Prof Lambert for taking the time to thoroughly review the manuscript and for imparting a particular fascination with measles, and Peter McIntyre for his detailed comments and guidance on the direction of the analysis and discussion. I would like to acknowledge Brynley Hull for his help in creating the incidence maps. I would like to acknowledge Catherine King for her guidance and assistance with literature search methodology. I would also like to acknowledge Kaitlyn Vette for her guidance on requesting extra NNDSS data fields, and the Australian Government Department of Health, CDNA, the Australian Institute of Health and Welfare, and the Australian Coordinating Registry for access to the data used.

Part One

Australian Vaccine Preventable Review Series: measles, 2012–2019

3.2 Abstract

Background: In 2014, the World Health Organization declared Australia had eliminated measles. Several measles immunisation policy and schedule changes have also occurred since 2014. We reviewed data sources relevant to measles epidemiology from 2012 to 2019 in this context.

Methods: Data on measles notifications, hospitalisations, and deaths were obtained from the National Notifiable Diseases Surveillance System, the National Hospital Morbidity Database, and the Australian Coordinating Registry. Data were analysed by age group, state/territory, Aboriginal and Torres Strait Islander status, genotype, place of acquisition, source of infection (importation status), and vaccination status.

Results: Between 2012 and 2019, 1,337 measles notifications (average annual notifications 0.7 per 100,000 per year) and 425 hospitalisations with measles as principal diagnosis (0.3 per 100,000 per year) were recorded. The highest annual notification rate was in 2014, when the rate in the Northern Territory was 21.4 per 100,000 per year. Although notification and hospitalisation rates were highest in infants <12 months (5.8 and 2.1 per 100,000 per year), people aged 10 to 39 years (10–19y: 272 notifications; 20–29y: 347; 30–39y: 266) accounted for 66% of notified cases. Of cases with a known vaccination status, only 20/169 (11.8%) aged 1–9 years had received at least one dose of measles-containing vaccine, compared with 215/571 (37.7%) of those aged 10–39 years. Persons born before 1966 (at least 47 years of age during the study period) are likely to have immunity from wild-type measles infection and had the lowest notification rates in each year. Of notified cases, 98.1% were imported or import related, and of the 900 measles viruses genotyped, D8 and B3 accounted for 89.1%.

Conclusion: Our findings of low measles incidence, with almost all cases imported or epidemiologically linked to an imported case, in the presence of robust surveillance, high two-dose measles vaccination coverage, provide evidence of continued elimination of endemic measles in Australia. Most cases eligible for vaccination are unvaccinated, which should remain the primary focus for prevention. Potential waning immunity in older age groups requires monitoring. Continued high population immunity and high-quality public health response to cases will be needed to maintain Australia's elimination status, particularly once international borders reopen.

3.3 Introduction

Measles virus is a highly infectious paramyxovirus that causes coryza, cough, fever, and a maculopapular rash.[1] Complications of infection can include pneumonia, encephalitis, otitis media, diarrhoea, and, rarely, subacute sclerosing panencephalitis.[1] It is estimated that more than 140,000 people died worldwide from measles in 2018, the majority of these being children younger than 5 years of age.[2]

Globally, the years from 2000 to 2016 saw an 88% decrease in annual measles incidence, with an increase in vaccination coverage with at least one-dose over this period from 72% to 85%.[3] However, incidence increased more than fivefold between 2016 and 2019 and endemic measles transmission was re-established in a number of countries in the Americas and Europe.[3] In 2019 widespread outbreaks of measles occurred in the Western Pacific region, including in Australia's near-neighbours (Samoa, New Zealand, Fiji, American Samoa, and Tonga).[4, 5] In 2012, the World Health Assembly (WHA) endorsed a target for measles elimination in five World Health Organization (WHO) regions by 2020, but this target was not met.[2] A formal commitment to measles eradication has been postponed by the WHA,[6] replaced by a goal of sustained elimination in all six WHO regions by 2030.[7]

In Australia, there was a peak in measles notifications and hospitalisations in the mid-1990s, followed by a decline to <1 per 100,000 per year in the 2000s.[8] This decrease was due to measures implemented under the 1998 National Measles Control Campaign, including a school-based vaccination program targeting 5–12 year old children, allowing for movement of the second dose of MMR from 11–13 years to 4–5 years of age.[8] Australia was certified by the WHO in 2014 as having achieved elimination of endemic measles,[9] although elimination was probably reached in the early 2000s.[10]

The last detailed review of measles epidemiology in Australia covered the period from 2000–2011.[8] Since then, as well as WHO certification of measles elimination, there have been substantial changes to immunisation policy impacting on the timing and coverage of measles-containing vaccines. In 2013 the second dose of measles-containing vaccine on the National Immunisation Program (NIP) schedule was moved to 18 months of age, given as the combination measles-mumps-rubella-varicella (MMRV) vaccine. MMRV replaced the second dose of measles-mumps-rubella (MMR) vaccine previously scheduled at 4 years of age, and the monovalent varicella vaccine dose previously scheduled at 18 months. In 2016, the federal government's No Jab No Pay policy was introduced, removing 'conscientious objection' exemptions from immunisation requirements to access a range of federal government family assistance payments.[11] At the same time, vaccination status

assessment time points for family assistance payments expanded from 1, 2, and 5 years only,[12] to annually up to 19 years of age.[13] Substantial catch-up vaccination activity was observed in the 2 years following the introduction of No Jab No Pay compared to baseline.[13]

With this study we aim to provide an updated review of measles epidemiology in Australia in the context of these issues, events and policy changes.

3.4 Methods

Notifications

Notification data were obtained from the National Notifiable Diseases Surveillance System (NNDSS). Data are collected by state and territory health departments under the provisions of the public health legislation in each jurisdiction and submitted to the Australian Government Department of Health on a daily basis for inclusion in the NNDSS.[14] Data included all notifications for confirmed or probable measles, as per the national case definition,[15] with an onset date (or where onset date was not available, the earliest of the specimen date, notification date, or notification received date) between 1 January 2012 and 31 December 2019.

Hospitalisations

Hospitalisation data were obtained from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database (NHMD), which contains line-listed, episode-level records for all hospital admissions in Australian public and private hospitals. Data included in this review were all hospitalisations with an admission date between 1 January 2012 and 31 December 2018 (latest full calendar year with data available) for which there was a principal or additional diagnosis code for measles (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modifications [ICD-10-AM] codes B05.0 [measles complicated by encephalitis], B05.1 [measles complicated by meningitis], B05.2 [measles complicated by pneumonia], B05.3 [measles complicated by otitis media], B05.4 [measles with intestinal complications], B05.8 [measles with other complications], or B05.9 [measles without complications]). The Aboriginal and Torres Strait Islander variable in this dataset is coded only as “Aboriginal and Torres Strait Islander” and “other”, with “other” including all other Australians and those not stated or unknown.

Mortality

Mortality data (line-listed cause of death unit record file data) were obtained from the Australian Coordinating Registry (ACR). We included deaths with a date of death between 1 January 2012 and

31 December 2018 with measles (ICD-10 code B05) recorded as the underlying or an associated cause of death. Counts <6 are expressed as a range to comply with the data release condition that small counts be suppressed in published reports.

Population estimates

Mid-year resident population estimates by age and jurisdiction of residence were obtained from the Australian Bureau of Statistics (ABS). ABS Aboriginal and Torres Strait Islander population projections for 2012–2019 were used. ABS mid-year resident population estimates at statistical area 3 (SA3) level were also used.

Data analyses

A descriptive analysis of the data was performed. Notifications were analysed by variables including: age, sex, state/territory of residence, place of acquisition (overseas/Australia), source of infection (importation status [imported or import-related]), whether recorded as hospitalised, geographical area (ABS statistical area 3 [SA3]), Aboriginal and Torres Strait Islander status and vaccination history. Vaccinations were deemed invalid if they were given within the 2 weeks prior to onset date and these cases were reported as unvaccinated if no other valid doses were recorded. Vaccinations reported without a vaccination date were included as valid. Hospitalisations were analysed by variables including: age, sex, jurisdiction, Aboriginal and Torres Strait Islander status, principal and additional diagnoses, and length of stay, with the main focus on hospitalisations with measles as the principal diagnosis. Age groups were assigned as follows: <1, 1–4, 5–9, 10–19, 20–29, 30–39, 40–49, and ≥50 years. Rates were calculated per 100,000 population per year using mid-year ABS resident population data, age-specific or jurisdiction-specific mid-year resident population data, or Aboriginal and Torres Strait Islander population projections as applicable. Summary statistics including median and range were calculated for age and length of hospital stay. Birth cohorts were selected based on key changes in immunisation schedules and identified levels of natural and vaccine acquired immunity in cohorts (Table 3.1). The 95% confidence intervals (CI) for birth cohort rates were calculated assuming a Poisson distribution.

Table 3.1. Immunisation schedule, immunity, and age band of birth cohorts

Birth cohort	Schedule and coverage	Age band during study (years)*
≤1965	Pre-vaccine era Natural immunity assumed	≥47
1966–1980	1 dose recommended/scheduled Assumed low to modest coverage†	32–53
1981–1999	2-dose schedule Variable 2-dose coverage: (68–92%)[16, 17]	13–38
2000–2011	2-dose schedule Higher 2-dose coverage: (93–94%)[18, 19]	1–19
≥2012	Dose 2 moved to 18 months High 2-dose coverage (95% in 2015)[20]	<1–7

* Age bands overlap due to ageing of individual birth cohorts across the years assessed.

† Coverage estimates not available from the literature for this age cohort.

Analysis was performed using Microsoft Excel 2010 and Stata 14.2 (Statacorp LLC, College Station, TX, USA). Maps were created using version 15 of the MapInfo mapping software.[21]

Ethics

This epidemiological review was approved by the Australian National University Human Research Ethics Committee (ANU/2020/63).

3.5 Results

Secular trends

There were 1,337 measles notifications between 2012 and 2019 (average annual rate 0.7 per 100,000 per year), and 474 hospitalisations between 2012 and 2018 with measles recorded in any diagnosis field, of which 425 (89.7%) had measles as the principal diagnosis (average annual rate 0.3 per 100,000 per year). There were peaks in measles notifications in 2014 and 2019 (Figure 3.1). Hospitalisations also peaked in 2014; data for 2019 were not available at the time of analysis.

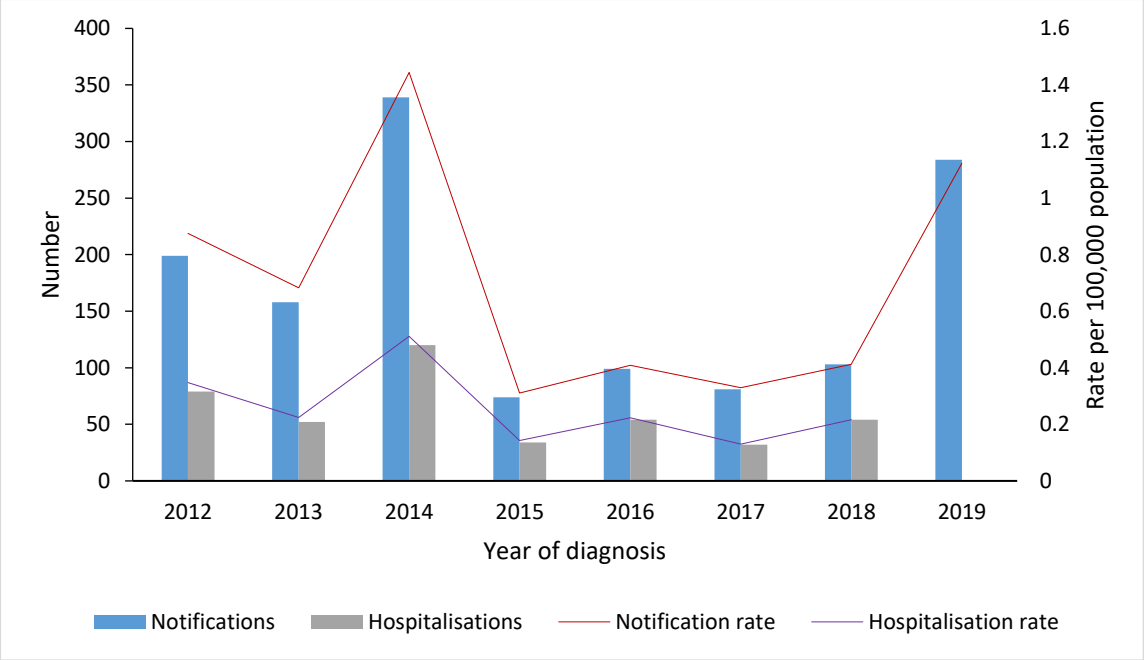


Figure 3.1. Number and rate per 100,000 population per year of measles notifications (2012–2019) and hospitalisations (principal diagnosis; 2012–2018; 2019 data not available), Australia
Data sources: National Notifiable Diseases Surveillance System, Australian Institute of Health and Welfare National Hospital Morbidity Database

Notification rate by jurisdiction

Notification rates varied within a narrow band across all jurisdictions except the Northern Territory (NT) during the study period. Apart from NT, where the peak incidence was 21.4 per 100,000 per year in 2014, peak incidence ranged from 1.0 in South Australia (SA) to 2.3 in New South Wales (NSW) and occurred in 2014 in all jurisdictions except NSW (2012), Western Australia (WA; 2019), and SA (2013), although incidence in 2014 was also above baseline in all of these states (Figure 3.2). The three most populous jurisdictions (NSW, Victoria, Queensland) accounted for 72.6% of all notified cases. The notification rate in NT in 2014 and 2019 was 10-fold higher than any other jurisdiction, with a total of 87 notifications across the study period, accounting for 6.5% of notifications compared with the 1% of the Australian population residing in NT. Hospitalisation rates were lower than notification rates and followed the same trends as notification rates for the years from 2012 to 2018 (2019 data not available).

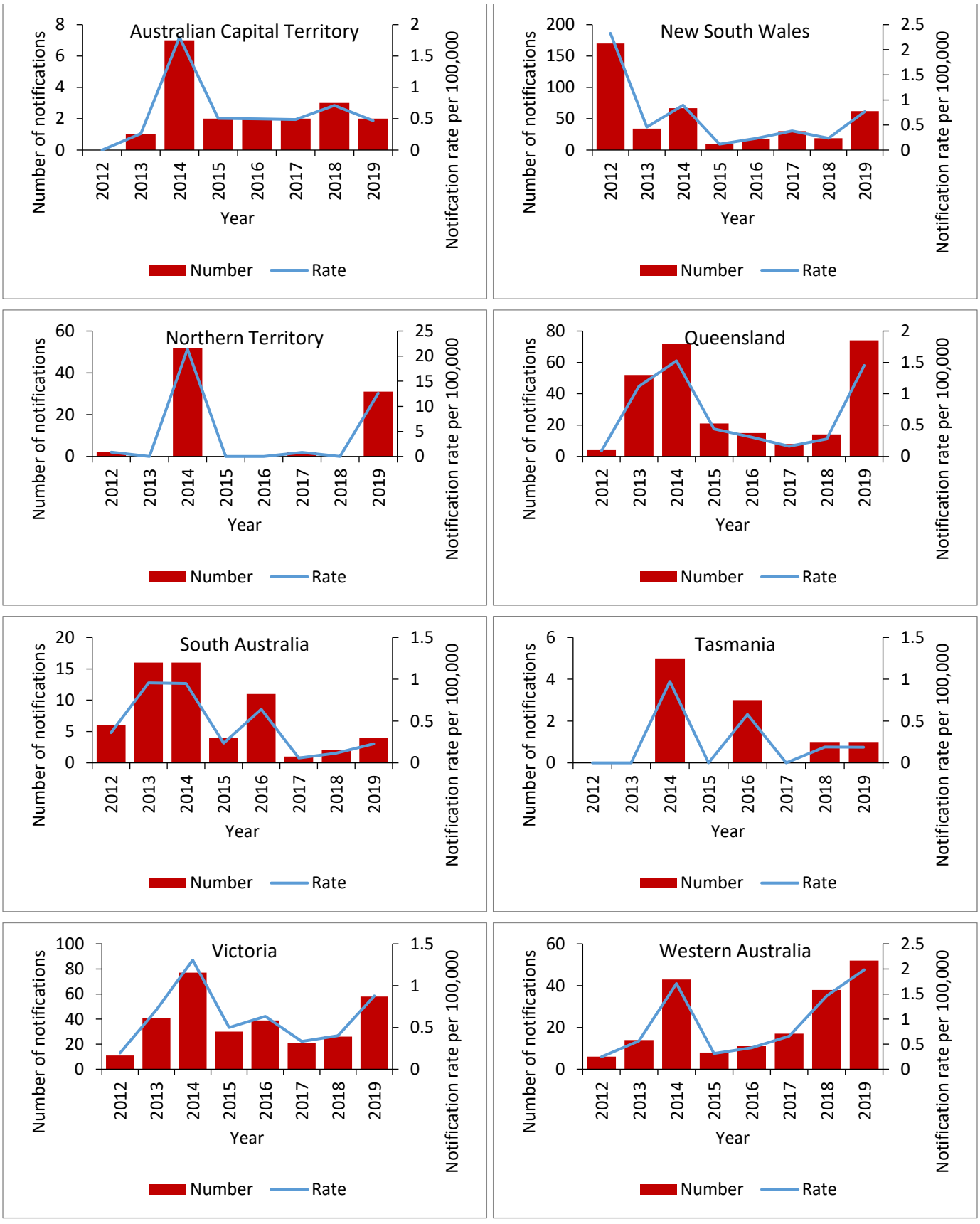


Figure 3.2. Measles notification count and rate per 100,000 per year by jurisdiction, Australia, 2012–2019

Note: scale used on the y-axis differs by jurisdiction

Data source: National Notifiable Diseases Surveillance System

Place of acquisition and importation status

Between 2012 and 2019, 486 (36.4%) notifications were recorded as overseas acquired (imported) and 837 (62.6%) as acquired in Australia (Table 3.2), with 14 (1.0%) without a documented country of acquisition or source of infection. Of the 837 cases acquired in Australia, 825 (98.6%) were import-related (epidemiologically linked to an imported case). The proportion of overseas acquired cases ranged from 10.6% in 2012 to 54.4% in 2018. Of the overseas acquired cases, over 90% were acquired in either the WHO South East Asia (n=220; 46.4%) or Western Pacific (n=208; 43.9%) regions. The most common countries of acquisition were Indonesia (n=106), Philippines (n=84), Thailand (n=52), India (n=41), and Vietnam (n=29). Of the 42 infants <12 months of age (29.6%) who acquired measles infection overseas, the youngest was aged 6 months.

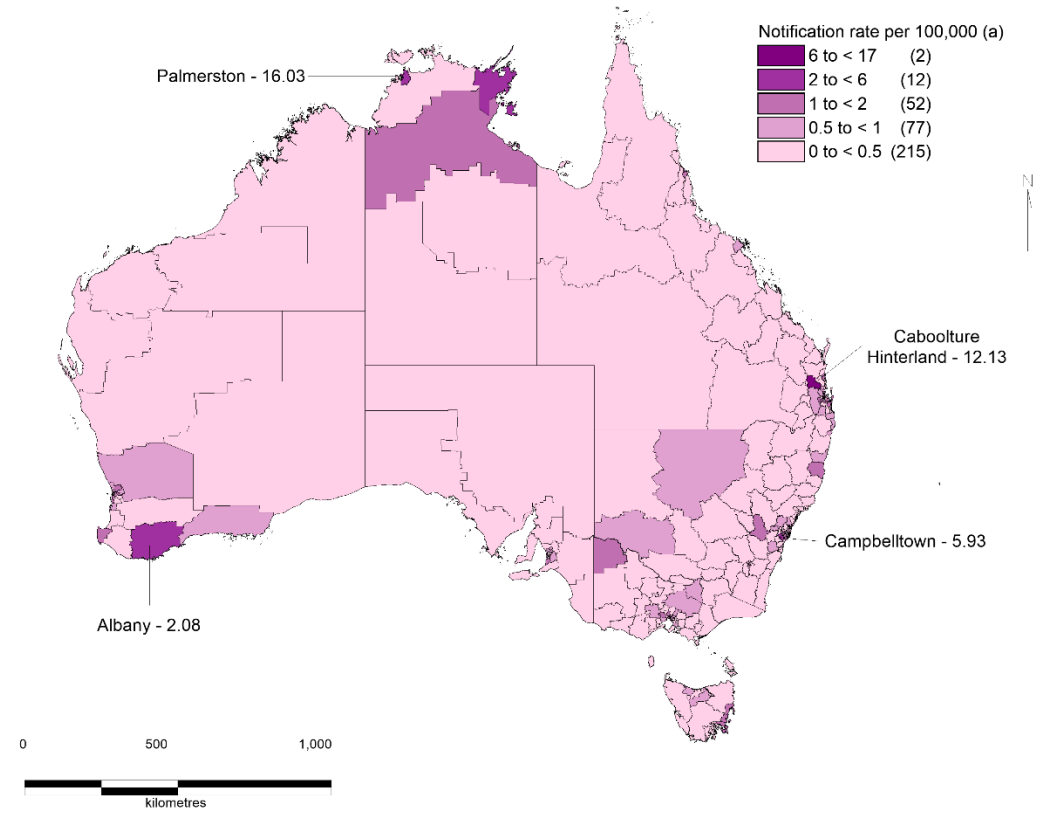
Table 3.2. Measles notifications by place of acquisition, importation status, and year, Australia, 2012–2019

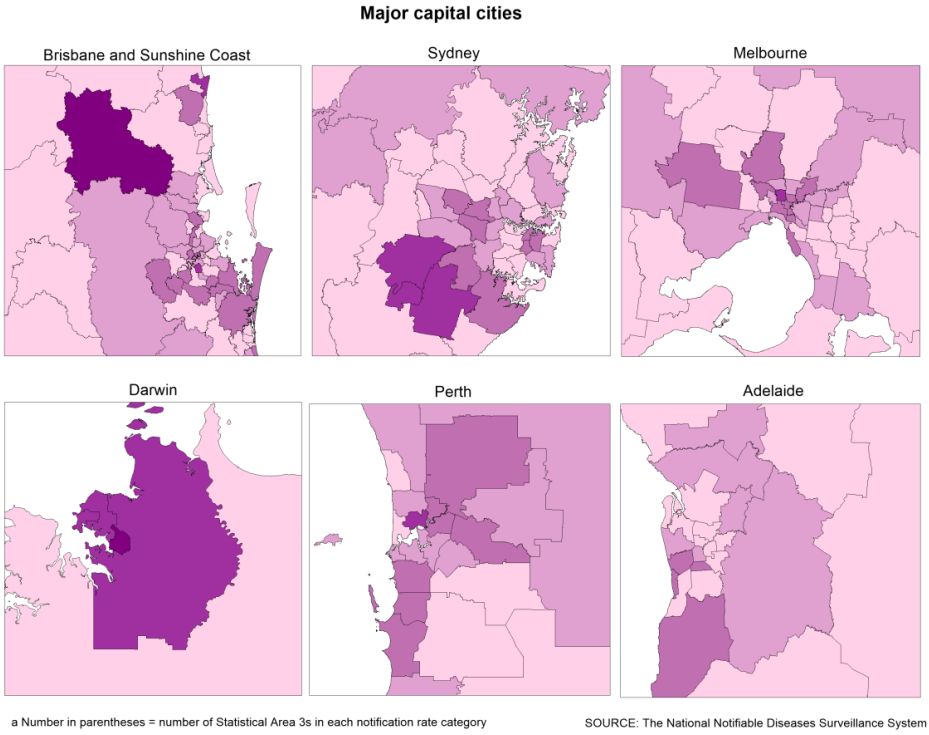
Year	Place of acquisition/importation status								Total
	Overseas		Australia				Unknown		
			Import-related		Unknown				
	n	%	n	%	n	%	n	%	n
2012	21	10.6	168	84.4	0	0	10	5.0	199
2013	51	32.3	107	67.7	0	0	0	0	158
2014	140	41.3	194	57.2	4	1.2	1	0.3	339
2015	35	47.3	39	52.7	0	0	0	0	74
2016	33	33.3	64	64.6	0	0	2	2.0	99
2017	38	46.9	41	50.6	1	1.2	1	1.2	81
2018	56	54.4	40	38.8	7	6.8	0	0	103
2019	112	39.4	172	60.6	0	0	0	0	284
Total	486	36.4	825	61.7	12	0.9	14	1.0	1337

Data source: National Notifiable Diseases Surveillance System

Small area analysis

Average annual incidence from 2012 to 2019 was <2 per 100,000 per year in 96.1% of SA3 areas (Figure 3.3). The highest incidence was in Palmerston (Northern Territory, 16.0 per 100,000 per year), followed by Caboolture Hinterland (Queensland, 12.1 per 100,000 per year), Campbelltown (New South Wales, 5.9 per 100,000 per year), and Litchfield (Northern Territory 4.2 per 100,000 per year). Incidence was 2–4 per 100,000 per year in 10 additional SA3 areas located in NSW (Bringelly-Green Valley, Camden), Northern Territory (Darwin City, Darwin Suburbs, East Arnhem), Queensland (Nathan, Noosa), Victoria (Brunswick-Coburg), and Western Australia (Albany, Perth City).





a Number in parentheses = number of Statistical Area 3s in each notification rate category

SOURCE: The National Notifiable Diseases Surveillance System

Figure 3.3. Measles notification rate (per 100,000 per year) by Statistical Area 3, Australia, 2012–2019

Seasonality

No consistent seasonal trend was evident in either notifications (2012–2019) or hospitalisations (2012–2018) (data not shown).

Genotype

Data on genotype were available for 67.3% (900/1,337) of notifications overall, with completeness increasing from 42.7% (85/199) in 2012 to a high of 82.5% (85/103) in 2018 before decreasing to 72.3% (206/284) in 2019 (Figure 3.4). Notably, 57.7% (45/78) of notifications with a missing genotype in 2019 were in the final quarter of the year. Genotype D8 was the most common genotype overall from 2012–2019 (526; 58.4% of cases genotyped) and was the most common genotype in all years except 2013 (D9; 33; 37.5%) and 2014 (B3; 153, 63.8%). Genetic diversity decreased between 2012 and 2019, with the prevalence of D4, D9, G3, and H1 all decreasing over time. B3 and D8 were the only detected genotypes in 2018 and 2019, and together made up 89.1% (802/900) of all known genotypes over the study period.

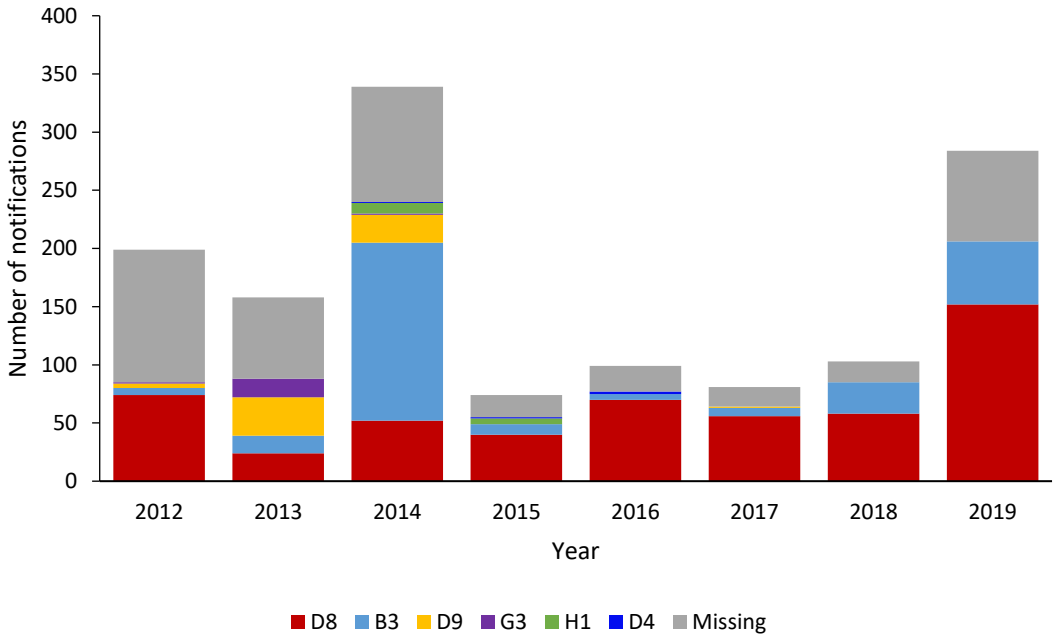


Figure 3.4. Proportion of measles genotypes among notifications by year, Australia, 2012–2019

Data source: National Notifiable Diseases Surveillance System

Age distribution

The highest age-specific notification rate was in infants aged <12 months across all years with an average annual incidence of 5.8 per 100,000 per year. The notification rate in infants was highest in 2012 (12.5 per 100,000 per year), with lesser peaks in 2014, 2018, and 2019 (Figure 3.5a). The second highest age-specific rate was in the 10–19 year age group early in the study period (2012–2014) but in the 20–29 year age group towards the end of the study period (2016, 2018–2019). The lowest incidence across all years was in people aged ≥50 years (<0.1 per 100,000 per year), followed by 40–49 years (0.4 per 100,000 per year).

The highest age-specific average annual rate of hospitalisations (principal diagnosis) was in infants ≤12 months (2.1 per 100,000 per year) (Figure 3.5b). The lowest average annual hospitalisation rate was in the ≥50 year age group (<0.1 per 100,000 per year), followed by the 5–9 year age group (0.1 per 100,000 per year). The age-specific notification to hospitalisation (principal diagnosis) ratios were as follows: 2.6 for ≤12 months, 1.6 for 1–4 years, 4.4 for 5–9 years, 4.5 for 10–19 years, 2.6 for 20–29 years, 2.2 for 30–39 years, 1.6 for 40–49 years, and 0.6 for ≥50 years.

Comparison of notifications recorded as hospitalised with NHMD hospitalisation data

Between 2012 and 2018, 187 notified measles cases were recorded in NNDSS as hospitalised, compared to the 474 hospitalisations (425 as principal diagnosis) recorded in the NHMD. The number of hospitalisations recorded in NNDSS were lower than in NHMD (principal diagnosis) in all jurisdictions except Western Australia, and the degree of discrepancy varied by jurisdiction. The age distribution of cases recorded as hospitalised in the NNDSS was similar to that of hospitalisations in the NHMD.

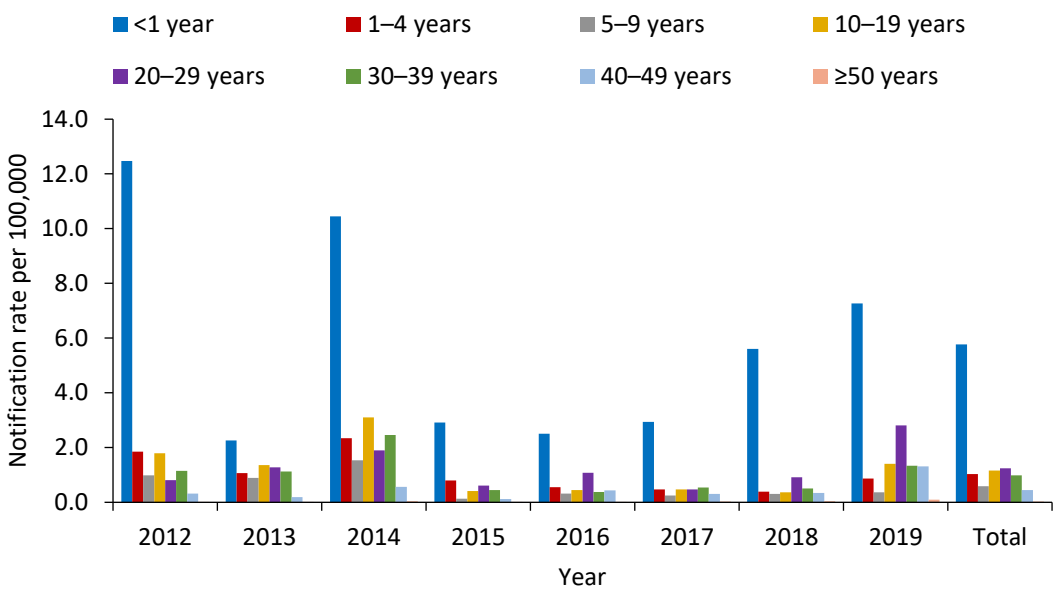


Figure 3.5a. Measles notification rate per 100,000 per year by age group, Australia, 2012–2019

Data source: National Notifiable Diseases Surveillance System

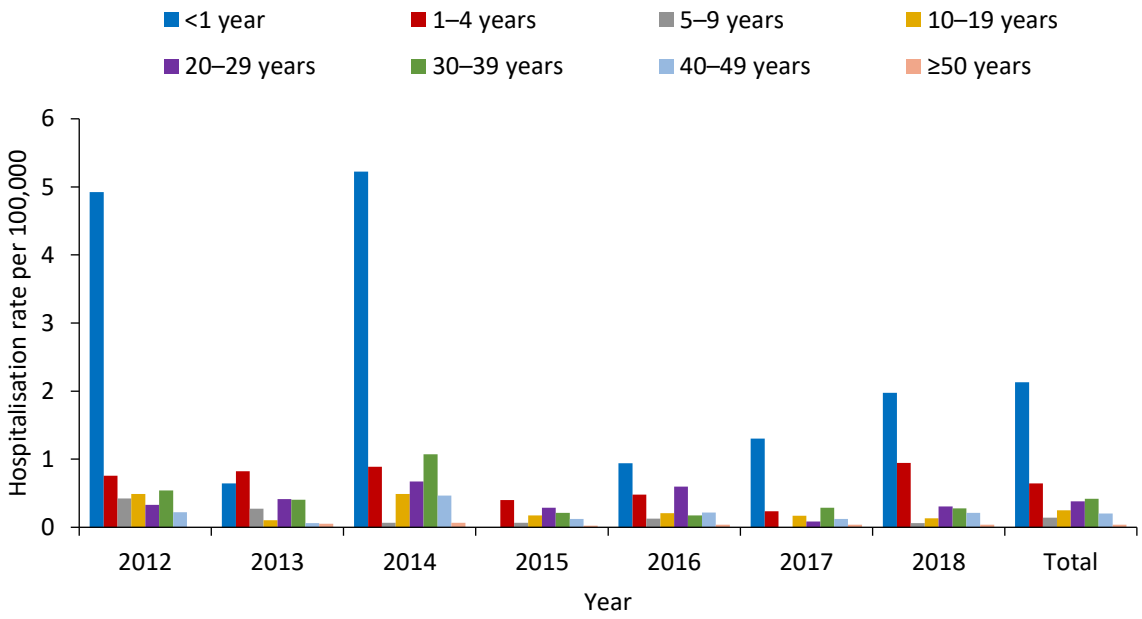


Figure 3.5b. Rate of measles hospitalisations (principal diagnosis) per 100,000 per year by age group and year, Australia, 2012–2018

Data source: Australian Institute of Health and Welfare National Hospital Morbidity Database

Birth cohort analysis

The measles notification rate in the birth cohort of children born from 2012 onwards was more than twice as high as any other birth cohort in 2014, but lower than the 1981–1999 cohort in 2019 (Figure

3.6). Notification rates between 2012 and 2019 were similar in the cohorts born between 1966 and 2011, and rates were consistently lowest in those born prior to 1966. The 1981–1999 cohort had the highest average annual rate between 2012 and 2019 (1.2 per 100,000 per year) once cases aged <12 months were excluded from the 2012 onwards cohort (Table 3.3).

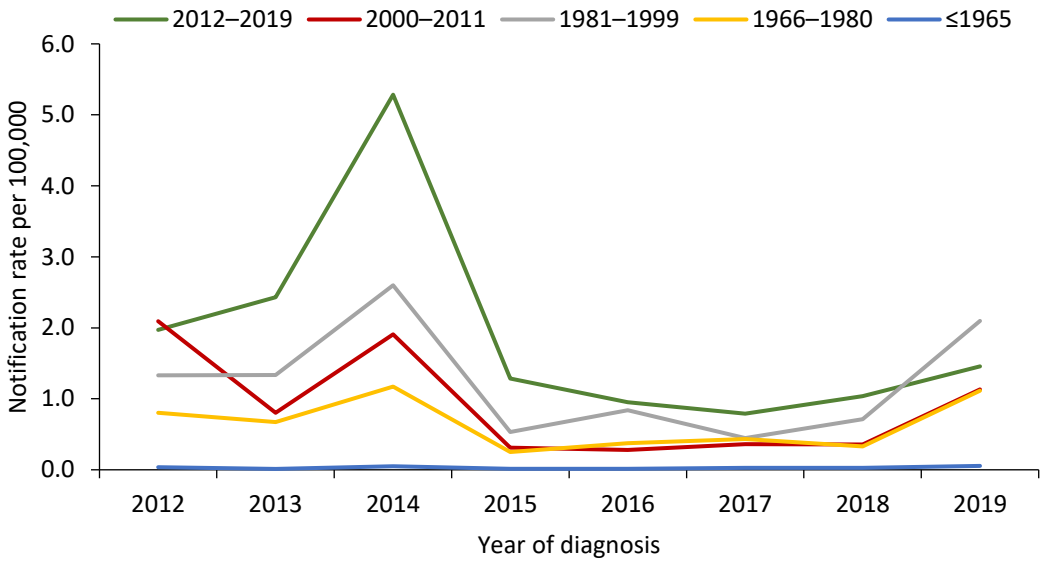


Figure 3.6. Measles notification rate per 100,000 per year by birth cohort and year of diagnosis, Australia, 2012–2019

Data source: National Notifiable Diseases Surveillance System

Table 3.3. Average rate of measles notification per 100,000 population per year by birth cohort, Australia, 2012–2019

Birth cohort (year)	Rate per 100,000 population per year	95% CI
≤1965	0.03	0.02–0.05
1966–1980	0.6	0.6–0.7
1981–1999	1.2	1.1–1.3
2000–2011 (rate including <12 month old cases)	0.9	0.8–1.0
2000–2011 (rate excluding <12 month old cases)	0.8	0.7–0.9
≥2012 (rate including <12 month old cases)	1.6	1.3–1.8
≥2012 (rate excluding <12 month old cases)	0.7	0.6–0.9

Data source: National Notifiable Diseases Surveillance System

Vaccination status by age group

Among cases aged 1–9 years, vaccination status was recorded in NNDSS for 169/175 (96.6%), of whom only 20 (11.8%) had received at least one dose of measles-containing vaccine (Table 3.4). Among cases aged 10–39 years with a known vaccination status (571/885; 64.5%), 37.7% had received at least 1 dose, with the proportion ranging from 30.8% in the 10–19 year age group (81.3% known vaccination status) to 43.9% in the 30–39 year age group (46.2% known vaccination status). At the other end of the age spectrum, infants younger than 12 months of age accounted for 142 cases (10.6%), and were all unvaccinated (Figure 3.7). Vaccination status was unknown for 50.0% (58/116) of cases aged 40–49 years, and 52.6% (10/19) of cases aged ≥50 years. Date of vaccination was missing for 59 (23.3%) of the 253 first doses and 5 (5.8%) of the 86 second doses recorded.

Table 3.4. Doses of measles-containing vaccine recorded for notified measles cases (where vaccination status known), by age group, Australia, 2012–2019

Doses recorded	Age group									Total
	<12m	12m–17m	18m–4y	5–9y	10–19y	20–29y	30–39y	40–49y	≥50y	
None	120	43	43	63	153	134	69	41	8	674
(%)	(100)	(89.6)	(82.7)	(91.3)	(69.2)	(59.0)	(56.1)	(70.7)	(88.9)	(72.7)
1	0	5	5	4	35	54	48	15	1	167
(%)	(0)	(10.4)	(9.6)	(5.8)	(15.8)	(23.8)	(39.0)	(25.9)	(11.1)	(18.0)
≥2	0	0	4	2	33	39	6	2	0	86
(%)	(0)	(0)	(7.7)	(2.9)	(14.9)	(17.2)	(4.9)	(3.4)	(0)	(9.3)
Total	120	48	52	69	221	227	123	58	9	927
(%)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

Data source: National Notifiable Diseases Surveillance System

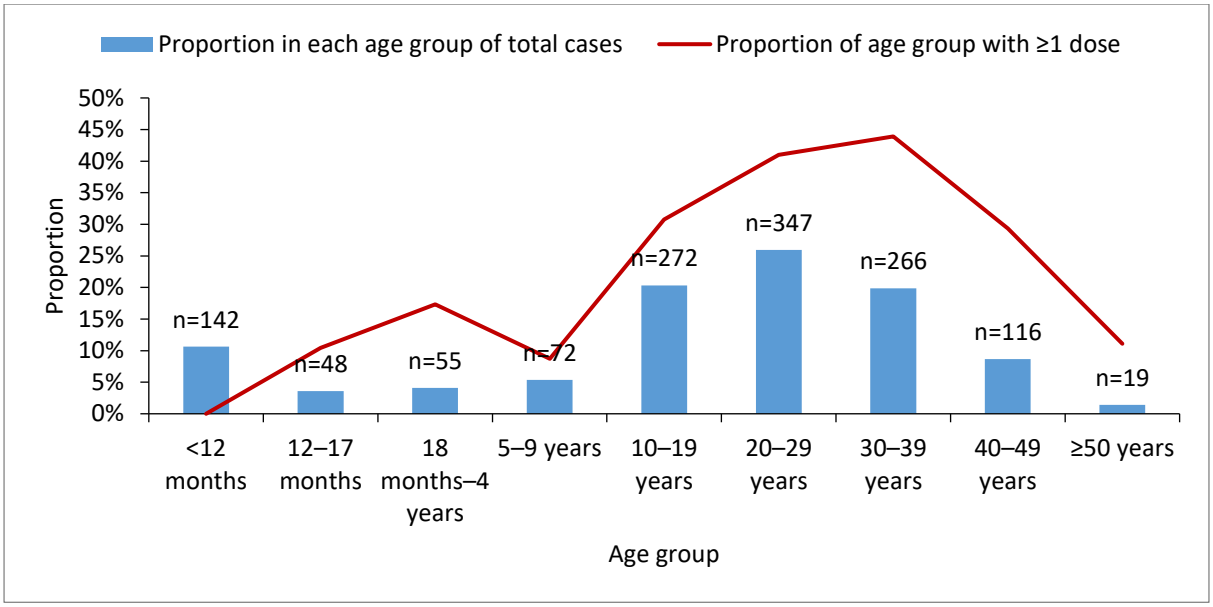


Figure 3.7. Proportion of total notified measles cases, and proportion in each age group with ≥1 dose of measles-containing vaccine recorded (where vaccination status known) Australia, 2012–2019
Data source: National Notifiable Diseases Surveillance System

Aboriginal and Torres Strait Islander status

Reporting of Aboriginal and Torres Strait Islander status was almost complete among measles notifications (97.7%), with 42 (3.1%) cases reported as occurring in Aboriginal and Torres Strait Islander people (average annual rate 0.7 per 100,000 per year). Aboriginal and Torres Strait Islander people accounted for 3.8% of hospitalisations (average annual rate 0.3 per 100,000 per year). This overall incidence of both notifications and hospitalisations across the study period was identical to that for the total population. Of notifications in Aboriginal and Torres Strait Islander people, 60.5% (n=26) were in individuals aged 10–39 years and 16.3% (n=7) in infants aged <12 months (median age 18 years; range 5 months–43 years).

Severe morbidity and mortality

Of the 425 hospitalisations with measles as principal diagnosis between 2012 and 2018, 79 (18.6%) had a recorded complication: 41 (9.6%) pneumonia; 10 (2.4%) encephalitis, meningitis, or intestinal complications; and 28 (6.6%) other complications. The proportion with a recorded complication was higher in older adults (15.2% in those aged 40–49 years, 30% in those aged ≥50 years), than in children (6.7% in those aged 5–9 years, 10.7% in those aged 1–4 years).

Hospitalisations with measles as the principal diagnosis accounted for 1,342 bed days, with a median length of stay of 3 days (range 1–20 days; Table 3.5). Adults and infants aged <1 year had a longer median length of stay (3–3.5 days), compared to children and adolescents (1–2 days).

Table 3.5. Number, rate per 100,000 per year and length of stay, measles hospitalisations (principal diagnosis), by age group, Australia, 2012–2018

Age group (years)	Hospital admissions		Length of stay (days)	
	N	Rate per 100,000 per year	Median	Range
<1	46	2.1	3	1–8
1–4	56	0.6	1	1–7
5–9	15	0.1	1	1–4
10–19	51	0.3	2	1–11
20–29	93	0.4	3	1–19
30–39	98	0.4	3	1–20
40–49	46	0.2	3.5	1–11
≥50	20	<0.1	3	1–14
Total	425	0.3	3	1–20

Data source: Australian Institute of Health and Welfare National Hospital Morbidity Database

Between 2012 and 2018, 1–5 deaths coded as due to measles (underlying or associated cause of death) were recorded in the cause of death data. No deaths were recorded in the hospitalisation or notification data.

3.6 Discussion

The incidence of measles in Australia remains low, although the average annual notification and hospitalisation rate (0.7 and 0.3 per 100,000 per year, respectively) in the 2012–2019 period was higher than for the 2000–2011 period (notification rate 0.4 per 100,000 per year; hospitalisation rate 0.2 per 100,000 per year).[8] Measles notification and hospitalisation rates in Aboriginal and Torres Strait Islander people were the same as overall population rates.

The highest age-specific notification (5.8 per 100,000 per year) and hospitalisation rate (2.1 per 100,000 per year) was in infants <12 months of age, who are not eligible for vaccination, first scheduled at 12 months. In elimination settings, infants become susceptible to measles earlier than 12 months of age due to waning of maternal antibodies in the absence of natural boosting.[22] The

next highest notification rates were in the 10–19 and 20–29 year age groups (1.2 per 100,000 per year), and the lowest rates in adults aged ≥40 years (<0.1–0.4 per 100,000 per year).

Measles is highly communicable, with a basic reproductive rate (R_0) between 9 and 18.[4] Therefore population immunity (either vaccine acquired or 'natural' immunity from wild-type measles virus infection) of 95% or higher across all age groups is required to prevent ongoing transmission.[4] While coverage of two doses of measles-containing vaccine recorded in the Australian Immunisation Register (AIR) in 2019 reached 93.3% at 2 years and 96.4% at 5 years,[20] coverage in older children and younger adults is lower.[23-25] Although coverage of two doses of measles-containing vaccine in adolescents aged 10–19 years increased from 86.6% to 89.0% at the national level during the two years following introduction of the federal No Jab, No Pay policy in 2016, this is still below the target of 95%.[13] Lower coverage in particular sub-populations can also increase the risk of outbreaks. The 2012 peak in notifications and hospitalisations in NSW was due to a sustained outbreak, centred on south-western and western Sydney, which disproportionately affected the 10–19 year age group and people of Pacific Islander descent.[26] Many Pacific Islander adolescents appeared to have missed routine childhood vaccinations, both before and after their arrival in Australia.[26] Data on vaccination coverage in young adults in the 20–29 year age group dates from the early period of operation of the AIR, and so are likely to be incompletely captured, but estimated childhood coverage in this age group is similar or slightly lower than 10–19 year olds.[17]

Analysis by birth cohort showed the lowest notification rate to be in the pre-1966 birth cohort (<0.1 per 100,000 per year), who were born before measles-containing vaccines were available and are known to have high levels of natural immunity.[27] The 1966–1980 birth cohort have lower levels of vaccination coverage than subsequent cohorts, due to the single-dose vaccination schedule in place until the addition of the adolescent dose in 1993, and less exposure to wild-type measles infection than the pre-1966 birth cohort.[27, 28] This age group was the target of an immunisation campaign in 2001 and 2002, although uptake was poor.[29] We found the measles notification rate between 2012 and 2019 was lower in the 1966–1980 cohort (0.6 per 100,000 per year) than later cohorts (1981–1999 cohort 1.2 per 100,000 per year; 2000–2011 0.9 per 100,000 per year), which could be due to lower levels of exposure, such as less frequent travel to endemic countries or lower-risk contact patterns when travelling. The notification rate in 2019 in the post-2012 birth cohort was similar to that in the 2000–2011 cohort and lower than the 1981–1999 cohort, which could reflect the impact of moving the second dose of measles-containing vaccine from 4 years to 18 months of age since 2013. However, age-specific trends may also be influenced by contact patterns affecting exposure during outbreaks.

Small area analysis showed that most areas with higher incidence were areas with documented measles outbreaks over the study period, including inner Melbourne (Brunswick-Coburg),[30] Greater Darwin (Palmerston, Litchfield, Darwin City, Darwin Suburbs),[31, 32] South West Sydney (Campbelltown, Bringelly-Green Valley, Camden),[26] South East Queensland (Caboolture Hinterland),[33] South West Western Australia (Albany),[34] and Perth (Perth City).[35] None of these areas had particularly low vaccination coverage in young children (2-dose MMR coverage was above 90% for all or most of the study period),[20, 36-39] although vaccination coverage is likely to have been lower in adults and coverage of 95% or more across all age groups is required to ensure herd immunity.[11] Noosa, on the Sunshine Coast, was the only area with both higher incidence and notably low coverage over the study period (2-dose MMR coverage in young children 84.5% in 2019), as well as high rates of vaccination objection (10.1% in 2012 and 6.6% in 2014), which may contribute to higher measles incidence observed. [20, 40, 41] Other reasons for higher incidence in some areas may include travel and contact patterns, population age structures, and stochastic factors.

Of cases notified between 2012 and 2019 with a known vaccination history, the proportion of those aged 1–9 years who had received at least one dose of measles-containing vaccine was 11.8%, compared to 37.7% of those aged 10–39 years. Although higher proportions of vaccinated cases are broadly consistent with what is expected in high-coverage settings,[42, 43] the higher proportion in the 10–39 year age groups could point a combination of under-vaccination and to waning immunity in those who were vaccinated. In sequential national serosurveys, antibody attrition has been observed with time-since-immunisation in age groups 5–34 years, presumed to be related to the absence of natural boosting in the elimination setting, although it is unclear whether this translates to increased susceptibility.[44] This age-related difference in vaccination status of cases may also be affected by recall biases in cases who were born before the AIR was established, whose vaccination history may not be well-recorded. The high proportion of cases aged 1–4 years who were unvaccinated (86.0 %) indicates that improving timeliness of the first dose of measles-containing vaccine should be a priority. The majority of cases aged ≥30 years had an unknown vaccination status, consistent with historical vaccinations in older age groups not being captured by the Australian Immunisation Register, which is the most reliable source for vaccination history records.

Of the 1,337 measles notifications recorded between 2012 and 2019, almost all (97.7%) were either imported or epidemiologically linked to an imported case. There were 42 cases of measles acquired overseas in children aged 6–11 months who were all unvaccinated. Infants travelling to measles-endemic countries can receive early vaccination as per Australian Immunisation Handbook guidelines, with the previous lower age limit of 9 months brought down to 6 months in April 2019 in

response to an increased number of cases in infants with a history of overseas travel.[45] Earlier vaccination may also be appropriate in outbreak settings. In response to a 2019 outbreak in the Northern Territory, the first dose of measles-containing vaccine was recommended at 9 months of age for children in the Darwin region until the outbreak had resolved.[32] Infants who receive a measles-containing vaccine early still require two further doses commencing from 12 months of age or a month after their initial dose, whichever is the later.[45]

The most common genotype in Australia from 2012–2019 was D8, followed by B3 and D9. These genotypes were also some of the predominant genotypes circulating over this period in the Western Pacific Region,[46] which accounted for 43.9% of overseas-acquired cases. D8 was also common in Thailand during this period,[9] while B3 has been endemic in the Philippines since 2013,[46] with both of these countries accounting for substantial proportions of Australia's overseas-acquired cases. The genetic diversity of measles globally has decreased due to improvements in control. Detected genotypes worldwide decreased from eight in 2009–2014 to four in 2018–2019, with 20 out of 24 measles genotypes now eliminated.[3, 47] This is reflected in the decreasing diversity of genotypes we found over the course of our study. The higher proportion of notifications without a recorded genotype in 2019, particularly from the fourth quarter, is likely due to COVID-19 pandemic related delays in testing.

The continuing low incidence of cases in Australia over this study period with nearly all being imported or epidemiologically linked to imported cases, in the context of relatively high vaccination coverage,[20] high-quality surveillance and response mechanisms, and sophisticated laboratory testing capacity[10] are consistent with maintenance of elimination. However, the 2014 and 2019 peaks in cases were a result of increased importations on a background of a global surge in cases in both years, including large outbreaks in Australia's Asia Pacific neighbours.[4, 9, 48] The causes of the resurgence of measles globally include weak immunisation systems, vaccine hesitancy, unidentified or unaddressed immunity gaps in older children and adults, and international travel facilitating spread of measles.[49] Australians travelling to endemic countries are therefore a particularly important target for prevention strategies. A 2013–2014 study of pre-travel health seeking behaviours of notified cases of imported infectious disease, including measles, found only 25% of cases overall, and 15% of cases who went on to develop a vaccine-preventable disease had sought pre-travel advice from a healthcare provider, primarily due to lack of awareness.[50] Jurisdictions have implemented media campaigns aimed at travellers in recent years,[51, 52] such as a NSW Health social media campaign in 2019 urging travellers to 'bring back memories, not measles', but the impact of these is unknown.[48]

In response to the COVID-19 pandemic, Australia closed its international borders to tourists in March 2020, and required all returning residents to quarantine for 14 days on arrival.[53] As of May 2021, no cases of measles had been reported nationally since these measures were implemented.[14, 54] While no impact on uptake of routine childhood immunisation as a result of the COVID-19 pandemic has been observed in Australia,[55] disruptions have occurred in many countries globally.[56] This poses a risk of large measles outbreaks internationally, and increasing importations to Australia once international travel restrictions are lifted. To maintain Australia's elimination status, sustained high vaccination coverage and robust surveillance and public health follow-up of cases will be needed.

This review has several limitations. Notification data may underestimate incidence, as not all cases seek health care, the diagnosis may be missed or diagnosed cases may not be notified. For measles, this is less likely due to its severity and the high level of public health scrutiny and follow-up of contacts. Hospitalisation data are prone to misclassification due to coding errors, particularly for rare diseases in age groups where they are uncommon,[57] which may explain the higher rate of measles hospitalisation compared to notification in the ≥50 year age group in our study. While NHMD hospitalisation data may overestimate the number of hospitalisations due to measles, notifications recorded as hospitalised likely underestimate the true number. Additionally, vaccination status was missing for a substantial proportion of notifications, largely as a result of childhood vaccination of adults born before 1996 not being captured in the AIR. Recorded vaccinations were missing a date of vaccination for 23.3% of first doses and 5.8% of second doses; some of these may have been given within the 2 weeks prior to disease onset and hence not appropriate for inclusion in our analyses. The case definition for measles notification was amended in mid-2019 with changes to the definitions of laboratory definitive, laboratory suggestive, and epidemiological evidence,[15] making the case definition slightly more sensitive, although these changes were minor and only applicable during the last 6 months of our study period. Hospitalisation data are episode-level records and may include multiple records for individual cases transferred between hospitals or readmitted. Completeness of Aboriginal and Torres Strait Islander status in hospitalisation data was not able to be assessed due to coding of the variable in the dataset. Assessment of the reliability of Aboriginal and Torres Strait Islander identification in the datasets utilised was outside the scope of the study.

3.7 Conclusion

Measles remains a rare disease in Australia. However, continued vigilant surveillance and public health response measures, along with sustained high vaccination coverage, will be needed to maintain elimination, particularly once international borders reopen.

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Part Two: Literature review

Effect of the COVID-19 pandemic on measles vaccination coverage in the South East Asia and Western Pacific Regions

3.9 Introduction

Substantial progress was made in global measles control between 2000 and 2016, with global incidence reducing by 88% and coverage of one dose of measles-containing vaccine (MCV1) increasing from 72% to 85%.[1] The Global Vaccine Action Plan, with the objective of eliminating measles in five of the six World Health Organization (WHO) regions by 2020, was endorsed by the World Health Assembly (WHA) in 2012.[2] Measles elimination has been a priority for the South East Asia Region (SEAR) and Western Pacific Region (WPR) with both having their own local targets for measles elimination.[3, 4] However, global progress towards measles elimination has stalled since 2018, with MCV1 coverage stagnating at 86%,[1] well short of the 95% target required to prevent ongoing endemic transmission. A global resurgence of measles occurred in 2018 and 2019, with large outbreaks occurring in Australia's Pacific neighbours, including New Zealand, Samoa, and Fiji.[5, 6] Factors contributing to the resurgence include declines in childhood immunisation coverage caused by conflict and population movement, increasing inequities in wealth and health, and misinformation driving vaccine hesitancy.[7]

The COVID-19 pandemic, beginning in early 2020, has since caused major disruptions to routine childhood immunisation services and mass vaccination campaigns globally, through pandemic mitigation strategies such as lockdowns, supply chain disruptions, and the diversion of health resources towards pandemic control.[8]

I aimed to review the literature to quantify the impact of this service disruption on measles vaccination coverage in countries in the South East Asia and Western Pacific Regions, where the majority of Australia's imported measles cases are acquired (see Chapter 3 Part One, Australian vaccine preventable disease epidemiological review series, measles, 2012–2019, page 57).

3.10 Methods

A systematic literature review was conducted to explore the impact of the COVID-19 pandemic on routine childhood measles vaccination coverage in the South East Asia and Western Pacific regions. The research question was as follows:

How has the COVID-19 pandemic affected measles vaccination coverage in countries in the South East Asia and Western Pacific regions?

The regions were defined using the World Health Organization region classification.[9]

The literature search was conducted using the Ovid Medline database. Search terms included immunisation and vaccination terms, measles and routine childhood immunisation terms, coverage

terms, COVID-19 terms, and Western Pacific and South East Asia terms, including terms for each country within those regions. The full search strategy can be seen in 3.13 Appendix B. Included were any papers that reported on measles vaccination coverage for any country in the SEAR or WPR, or on the SEAR and WPR on a regional level from 1 January 2020 to 22 September 2021.

A grey literature search was also conducted in the UNICEF and WHO websites, searching for measles with date restrictions since 1 January 2020, but did not yield any additional articles eligible for inclusion.

3.11 Results

The search yielded 44 results, five of which were included (Figure 3.8). Results were excluded for the following reasons: related to countries outside the SEAR and WPR (n=3), reported on service disruption but not coverage (n=2), related to COVID-19 epidemiology and vaccines (n=12), reported on pre-pandemic coverage (n=3), reported on coverage of other vaccine antigens (n=4), reported on vaccine hesitancy (n=4), reported on the effect of other vaccinations on COVID-19 (n=8), reported on general immunisation program considerations (n=2), and quantified impact of various coverage scenarios on disease rates without estimating coverage (n=1).

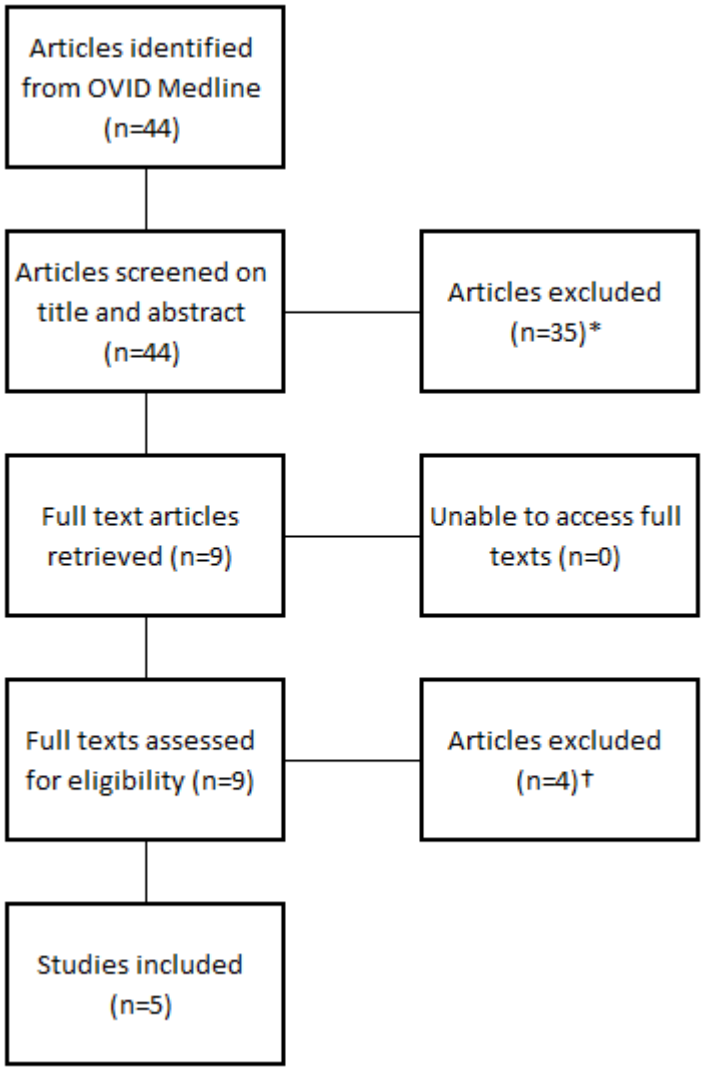

Figure 3.8. Flow diagram of the inclusion and exclusion of literature search results

* Articles including countries outside of SEAR and WPR (n=3), COVID-19 epidemiology and vaccines (n=12), pre-pandemic coverage (n=3), coverage of other vaccine antigens (n=4), vaccine hesitancy (n=4), effect of other vaccinations on COVID-19 (n=8), general immunisation program considerations (n=1)

† Articles on disruption to service delivery only (n=2), estimating disease burden assuming reduced coverage (n=1), general immunisation program challenges (n=1)

Synthesis of findings

Of the five articles included in this literature review (3.13 Appendix A), two included data on countries in WPR only[10, 11] and one on a SEAR country only.[12] Two of these studies, Aizwa et al[10] and Zhong et al,[11] were retrospective observational studies assessing administrative coverage by month

in 2020 compared to previous years. The third study by Jain et al[12] was a cross sectional survey to parents regarding immunisation status of children in the target population. The two final included studies, Causey et al[13] and Harris et al,[14] were international studies, with one including data on SEAR and WPR at the regional level,[14] and one being a global study reporting on regions as well as by individual countries.[13] Causey et al[13] modelled the estimated effect of the COVID-19 pandemic on vaccination coverage, based on administrative data on number of administered vaccine doses reported by countries to the WHO compared to the expected number from the Global Burden of Diseases, Injuries, and Risk Factors study (GBD) 2020 vaccine coverage models. The Harris et al[14] article was a cross sectional study conducted by Sanofi Pasteur, a vaccine manufacturer, in which Sanofi Pasteur medical teams answered surveys on service disruption and coverage using a combination of publicly available data, press releases, clinician interactions, and sales data.

Japan

Aizwa et al[10] assessed administrative coverage by comparing the number of first dose measles-containing vaccine (MCV1) and second dose measles-containing vaccine (MCV2) that were administered in four cities between January and September 2020 by month, compared to the average number of doses administered by month from 2016 to 2019. MCV1 is given at 12 months and MCV2 is given at 5–6 years of age in Japan. The number of vaccine doses administered in March and April 2020 decreased across both age groups in all four cities. Administered doses of MCV1 were lowest (25% fewer vaccinations compared to 2016–2019) in April in Fuchu city, while MCV2 reached a low of 40% fewer vaccinations in March 2020 in Kawasaki city. Vaccination catch-up activity was observed for MCV2 in the 5–6 year age group from June 2020, while administered MCV1 doses remained lower than previous years at the end of the study period.

Causey et al[13] found that Japan was projected to reach an estimated 98.0% (95% confidence interval [CI] = 94.9–99.5%) MCV1 coverage in the absence of the COVID-19 pandemic but that estimated national MCV1 coverage in Japan accounting for COVID-19 disruptions was instead 91.5% (95% CI = 54.5–99.2).

India

Causey et al[13] found that the expected coverage of MCV1 in India in the absence of the COVID-19 pandemic was 95.1% (95% CI = 89.4–98.1), and this fell to an estimated 85.7% (95% CI = 80.5–89.1) when accounting for the effects of the pandemic.

Jain et al[12] conducted telephone surveys with the guardians of 2,144 children that turned 1 year of age between January and October 2020 and compared the immunisation status between children

that were due immunisations before (unexposed), partly during (partially exposed), entirely during (heavily exposed), and after (post-exposure) the national lockdown. While not reporting on measles coverage specifically, the coverage of complete first year immunisations (defined as three doses of pentavalent vaccine [diphtheria, pertussis, tetanus, hepatitis B, and *Haemophilus influenzae type b* antigens] and MCV1) was 74.5% in those who were unexposed, 70.4% in the partially exposed, and 64.1% in the heavily exposed, while coverage in the post-exposure group improved to 71.0%. These estimates are lower than those reported by Causey et al and may reflect the population in which the study was conducted, which included only families participating in a state-wide government health insurance program, who are among the country's poorest. It may also reflect the difference between measles coverage alone and fully immunised at 1 year old coverage, which includes three pentavalent doses. When looking at timeliness, the heavily exposed group were more likely to have received MCV1 at an older age, suggesting some successful catch-up activity.

Singapore

Zhong et al[11] conducted a multicentre retrospective cohort study comparing the number of vaccine doses administered by month from January to April 2020, compared to the same months in 2019. Compared to 2019, they found a 25.6% decline in uptake of MCV1 in polyclinics (public primary care clinics), 57.3% decline in hospitals, and 73.6% decline in private clinics. The authors also modelled the impact of the reduction on coverage among 1–2-year-old children, estimating that coverage may have dropped to 84% from a baseline of 95.6%.

These findings are consistent with the modelling by Causey et al,[13] which estimated MCV1 coverage in Singapore accounting for COVID-19 related disruptions to be 83.0% (95% CI = 47.0–94.5).

SEAR and WPR

Harris et al[14] calculated the median absolute percentage reduction in vaccine coverage rates for measles in school-entry aged children in four unnamed countries in the SEAR and WPR. They reported the median absolute percentage reduction in vaccine coverage to be 9% (IQR 3–31).

Among the GBD super-regions, Causey et al[13] found that the largest modelled declines in MCV1 were in South Asia, with administered doses of MCV1 falling by 43.1% (95% CI = 42.1–44.1) in April compared to expected uptake. The coverage of MCV1 in South Asia in 2020 was estimated to be 84.6% (95% CI = 80.1–88.0), down from the 91.6% (95% CI = 86.9–94.8) expected in the absence of the COVID-19 pandemic. The WPR was not reported separately, but the expected coverage of MCV1 in the absence of the COVID-19 pandemic in South East Asia, South Asia, and Oceania combined was estimated at 90.8% (95% CI = 88.1–93.0), while the estimated coverage accounting for the pandemic

was 84.3% (95% CI = 67.6–88.7). There was some improvement later in the year, with monthly administration of MCV1 in South Asia nearing expected levels by the end of 2020. However catch-up was not complete, with annual MCV1 administration still 13.0% lower than expected for 2020.

3.12 Conclusions

All studies reported a substantial decline in coverage in 2020. These may underestimate the overall effects of the COVID-19 pandemic on measles coverage, as there are no studies published yet on the continuing impact of the pandemic into 2021 on routine childhood immunisation coverage. This may be particularly pertinent for countries like India, where a devastating second wave in 2021[15] is likely to have caused substantially larger declines in coverage than those reported in 2020. An additional limitation is that these studies may have been conducted in areas where coverage was known to be impacted, and may not be representative of the whole population, especially rural areas which may have been less affected by COVID-19 and pandemic mitigation measures. Additionally, studies conducted over short time frames in 2020 are not able to distinguish between missed and postponed doses, and the use of administrative data may miss catch-up vaccination activity that occurred outside the target population age.

Australia was verified as having achieved measles elimination in 2014. However, maintenance of Australia's measles elimination status is not guaranteed. The United Kingdom (UK) achieved measles elimination in 2017, but subsequently lost the status in 2019 due to importations of measles and low MCV2 coverage leading to endemic spread.[16] An additional three European countries lost their elimination status in 2019: Czechia, Greece, and Albania.[17] The United States (US) has so far retained its elimination status, achieved in 2000, but a pair of outbreaks in 2019 lasting nearly a year warn of the possibility of the re-establishment of endemic measles in the US, if underlying challenges around access, misinformation, and vaccine hesitancy continue.[18-20]

The potential resurgence of measles in the SEAR and WPR due to declines in coverage related to the COVID-19 pandemic has implications for Australia's measles control. Between 2012 and 2019, 98.6% of all measles cases in Australia were either documented to be imported or import-linked, and among imported cases, 46.4% were imported from SEAR and 43.9% were imported from WPR. India was among the top five countries from which measles cases in Australia were imported (see Chapter 3 Part One, Australian vaccine preventable disease epidemiological review series, measles, 2012–2019, page 57). Amid warnings about the impact of the COVID-19 pandemic on measles elimination efforts internationally,[21, 22] Australia will need to ensure uptake of routine measles immunisation remains high and robust surveillance and public health follow up of cases is maintained to retain its elimination status.

3.13 Appendices

Appendix A. Summary of data from five articles that met literature search inclusion criteria

Author Year [Ref #]	**Setting** **Study type**	**Study period**	**Vaccination data sources**	**Reported impact on coverage**
Aizawa 2021 [10]	Japan (Kawasaki City, Fuchu City, Niigata City, Nagasaki City) Retrospective observational study	January to September 2020	Administrative Vaccine records from Kawasaki and Niigata health centres, Nagasaki municipal office, and the Fuchu City Medical Association.	• MCV1: low of 15% fewer vaccinations in February 2020 compared to 2016–2019 • MCV2: low of 40% fewer vaccinations in March • Catch up activity observed by June among 5–6 year old children
Causey 2021 [13]	Global Modelling study	January to December 2020	Administrative Country reported data on the monthly number of doses of vaccine administered between January 2019 and December 2020	• South Asia: MCV1 decline peaked at 43.1% (95% CI 42.1–43.1%) fewer vaccinations in April. Coverage expected to be 91.6% (95% CI 86.9–94.8) but estimated at 84.6% (95% 80.1–88.0). • South Asia, South East Asia, and Oceania: expected coverage 90.8% (95% CI 88.1–93.0), estimated coverage after COVID: 84.3% (95% CI 67.6–88.7) • Recovery in second half of 2020
Harris 2021 [14]	South-East Asia and Western Pacific Cross-sectional study	February to 1 June 2020	Survey to Sanofi Pasteur medical teams Sanofi Pasteur medical teams used publicly available data where available, or otherwise sales data, press releases, or clinician interactions	• 9% reduction in vaccine coverage rates for school-entry aged children

Author Year [Ref #]	Setting Study type	Study period	Vaccination data sources	Reported impact on coverage
Jain 2021 [12]	Rajasthan, India Cross-sectional survey	January to October 2020	Household survey to children turning 1 between Jan and October 2020 Vaccination record cards consulted where available	• First year immunisation: 74.5% among unexposed, 70.4% among partially exposed, 64.1% among heavily exposed. • Heavily exposed more likely to have received measles older, evidence of successful catchup
Zhong 2021 [11]	Singapore Retrospective observational study and modelling study	January to April 2020	Administrative Number of vaccine doses administered by month at each site: five public primary care clinics (polyclinics), one paediatric outpatient clinic (hospital), and three private paediatrician practices (private clinics).	• January to March 2020: drop of 5.5% in polyclinics and hospitals compared to 2019, and 52.2% decline in private clinics. • April: decline of 25.6% in polyclinics compared to 2019, and 57.3% in hospitals, and 73.6% in private clinics • Model suggests that measles coverage in 1–2 year-old children at the end of May 2020 to be 84% (from 95.6% previously) • If trends continue for whole of 2020, coverage will drop to 74%

Appendix B. Literature review search strategy

No.	Search term	Results
1	exp Immunization/	187355
2	exp Immunization Programs/	14929
3	exp Vaccines/	245008
4	(immunis$ or immuniz$ or vaccin$).tw.	423588
5	1 or 2 or 3 or 4	525932
6	exp Measles/	16132
7	exp Measles virus/	6615
8	exp Measles-Mumps-Rubella Vaccine/	2921
9	exp Measles Vaccine/	9283
10	measles$.tw.	24477
11	((routine$ or child$) adj2 (immunis$ or immuniz$ or vaccin$)).tw.	20024
12	epi.tw.	22025
13	(national adj (immunis$ or immuniz$) adj program).tw.	935
14	nip.tw.	1617
15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	70380
16	5 and 15	35063
17	exp Vaccination Coverage/	1773
18	(cover$ or uptake).tw.	797488
19	status.tw.	935588
20	rate$.tw.	3086938
21	(underimmun$ or under-immun$ or undervaccin$ or under-vaccin$).tw.	2453
22	(suboptimal$ or sub-optimal$ or full$).tw.	905023
23	17 or 18 or 19 or 20 or 21 or 22	5197894
24	16 and 23	15574
25	exp Pacific Islands/	63572
26	(west$ adj3 pacific).tw.	3832
27	(pacific adj3 (island$ or countr$ or region$ or zone$)).tw.	12314
28	PICs.tw.	1177
29	exp Papua New Guinea/	3592
30	(papua adj new adj guinea$).tw.	4932
31	PNG.tw.	1163

32	exp Samoa/	806
33	samoa$.tw.	1446
34	exp New Zealand/	41744
35	(new adj zealand).tw.	56978
36	exp Asia, Southeastern/	103568
37	("south east asia" or "south-east asia" or "southeast asia").tw.	14514
38	exp Indonesia/	11936
39	indonesia$.tw.	17213
40	exp Philippines/	8887
41	philippine$.tw.	10742
42	exp Thailand/	28211
43	thailand$.tw.	29689
44	exp India/	110903
45	india$.tw.	176414
46	exp Vietnam/	13403
47	vietnam$.tw.	20222
48	exp Singapore/	14516
49	singapore$.tw.	17871
50	exp Malaysia/	16476
51	malaysia$.tw.	21532
52	exp Japan/	144667
53	japan$.tw.	232511
54	(hong adj kong).tw.	21327
55	exp China/	227674
56	china$.tw.	222470
57	exp Mongolia/	1922
58	mongolia$.tw.	9738
59	exp "Republic of Korea"/	36355
60	(south adj korea$).tw.	15446
61	exp Bangladesh/	12382
62	bangladesh$.tw.	17082
63	exp Nepal/	9440
64	nepal$.tw.	12393

65	exp Sri Lanka/	6479
66	(sri adj lanka$).tw.	8034
67	exp Bhutan/	563
68	bhutan$.tw.	1082
69	exp Myanmar/	2839
70	myanmar$.tw.	3884
71	maldives.tw.	382
72	exp Timor-Leste/	241
73	((timor adj leste) or timor-leste or timorleste).tw.	382
74	(east adj timor).tw.	206
75	timor$.tw.	979
76	exp Cambodia/	3567
77	cambodia$.tw.	5178
78	exp Brunei/	253
79	brunei$.tw.	480
80	(solomon adj island$).tw.	924
81	exp Taiwan/	40742
82	taiwan$.tw.	51330
83	exp Tonga/	259
84	tonga$.tw.	723
85	exp Vanuatu/	384
86	vanuatu$.tw.	706
87	exp Laos/	2077
88	lao$.tw.	5351
89	exp Fiji/	1028
90	fiji$.tw.	2433
91	(new adj caledonia$).tw.	1774
92	exp New Caledonia/	932
93	exp Brunei/	253
94	((brunei adj darussalam$) or brunei$).tw.	480
95	exp Polynesia/	10891
96	niue$.tw.	121
97	exp Palau/	204

98	palau$.tw.	496
99	(cook adj island$).tw.	288
100	(french adj polynesia$).tw.	1104
101	exp Pitcairn Island/	13
102	(pitcairn adj island$).tw.	22
103	exp Guam/	713
104	guam$.tw.	1489
105	exp "Democratic People's Republic of Korea"/	253
106	(north adj korea$).tw.	570
107	exp Micronesia/	2070
108	kiribati$.tw.	214
109	tokelau$.tw.	114
110	exp Macau/	291
111	(macao$ or macau$).tw.	893
112	tuvalu$.tw.	81
113	(marshall adj island$).tw.	337
114	micronesia$.tw.	951
115	polynesia$.tw.	2516
116	nauru$.tw.	192
117	or/25-116	1176824
118	24 and 117	2802
119	exp COVID-19/	106949
120	exp SARS-CoV-2/	83237
121	('2019 nCoV$' or 2019-nCoV$ or 2019nCoV$ or 'n CoV$' or n-CoV$ or nCoV$).tw.	1907
122	('covid 19' or covid-19 or covid19).tw.	151732
123	('SARS CoV2' or SARS-CoV2 or SARSCoV2 or SARS-CoV-2).tw.	51332
124	119 or 120 or 121 or 122 or 123	175561
125	118 and 124	44

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Chapter 4

The epidemiology of diphtheria in Australia, 1999–2019

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4.1 Prologue

Background

I inherited this diphtheria epidemiological review project from Dr Caitlin Swift, a public health officer trainee, whose rotation at NCIRS finished in January 2020. Dr Swift was unable to complete the project as the data required for the review had not been provided in time. The project was then further delayed by the COVID-19 Schools Study.

This project was of special interest to me, as before beginning the MAE, my previous role had been in responding to a diphtheria outbreak in Yemen.

My role

I was handed over this project with a protocol already written and ethics approval from the Australian Capital Territory (ACT) Human Research Ethics Committee (HREC). I took lead of the study, reviewed the protocol, updated the personnel, submitted an update and extension request for the ACT ethics approval, and submitted an ethics approval request to the Australian National University HREC. I updated the requests to include the most recent available data, conducted a literature review, performed the data analysis, and completed the write up of the study.

I also liaised with jurisdictional members of the National Surveillance Committee to confirm site of infection for notifications missing these data.

Public health impact

Key to public health surveillance is the analysis and interpretation of collected data for public health action. It was noted in the 2012–2015 Vaccine Preventable Diseases Summary report that cases of diphtheria had increased compared with the previous decade. Although still a very rare disease, the cause of this increase warranted investigation.

Due to the rarity of diphtheria, the notification dataset was small. Nevertheless, there were substantial missing data, particularly in the site of infection field, which is not a mandatory field for diphtheria in the National Notifiable Diseases Surveillance System (NNDSS). As the case counts were small, I was able to liaise directly with jurisdictions to clarify site of infection for records with missing data, and feed that back into the NNDSS to improve data quality. This also facilitated a discussion between the jurisdictions and the Commonwealth about routine reporting of site of infection in the future.

This resulting manuscript was submitted to the Commonwealth Department of Health and submitted to *Communicable Diseases Intelligence*.

Lessons learnt

This was the first project that I began as a principal investigator. I learnt how to submit ANU ethics applications, and how to manage different feedback from supervisors. I also learnt how to best set up my data analysis and exploratory data tables, and how to use population denominators in calculation of average annual rates. However, as the measles epidemiological review was a deliverable with a deadline to the Department of Health, I deferred the write-up of this Chapter until after submission of the measles work and was therefore able to apply what I had learnt in the measles review about structure and voice, and how to focus a discussion to this Chapter. I also used this manuscript as my submission for a Scientific Writing Workshop run out of NCIRS, in which each participant presents a manuscript which is then critically evaluated by peers. This workshop was very useful, particularly in clarifying my thinking about how to manage the different presentations of diphtheria within one manuscript.

Acknowledgements

I would like to acknowledge and thank all my field and academic supervisors for time spent reviewing and providing comments on this work. I would especially like to thank A/Prof Lambert for helping me to liaise with jurisdictions regarding missing data, and jurisdictional National Surveillance Committee members for providing those data. I would like to acknowledge Dr Caitlin Swift for her efforts in getting this project off the ground. I would also like to acknowledge the Australian Government Department of Health, Communicable Diseases Network Australia, the Australian Institute of Health and Welfare, and the Australian Coordinating Registry for access to the data used in this review.

4.2 Abstract

Background: Diphtheria is rare in Australia, but an increasing number of cases have been notified in recent years. Alongside notifications from 1999 to 2019, we analysed other relevant national data sources to evaluate trends over the past two decades.

Methods: Diphtheria notifications (National Notifiable Diseases Surveillance System [NNDSS]), hospitalisations (National Hospital Morbidity Database) and deaths (Australian Bureau of Statistics and the Australian Coordinating Registry) were separately analysed by site of infection, age group, sex, state/territory, Aboriginal and Torres Strait Islander status, and vaccination status.

Results: During the study period, eight (0.002 per 100,000 per year) cases of respiratory diphtheria and 38 (0.008 per 100,000 per year) cases of cutaneous diphtheria were recorded in the NNDSS, with 45/46 reported in the nine years since 2011. *Corynebacterium diphtheriae* accounted for 87% of notified cases, who had a median age of 31.5 years (respiratory diphtheria) and 52.5 years (cutaneous diphtheria); no respiratory diphtheria was notified <15 years of age. Almost twice as many cutaneous (71%) than respiratory cases (38%) were acquired overseas. Rates of both presentation types were higher in Aboriginal and Torres Strait Islander people (respiratory: 0.007 per 100,000 per year; cutaneous: 0.021 per 100,000 per year) compared to rates in the overall population. Queensland had the highest rate of notified respiratory cases (0.007 per 100,000 per year), and the Northern Territory the highest rate of cutaneous notifications (0.043 per 100,000 per year). There were 29 hospitalisations with a principal diagnosis diphtheria code in the NHMD between 2002 and 2018, of which eight were designated as respiratory (0.002 per 100,000 per year), eight as cutaneous (0.002 per 100,000 per year), and 13 had an unknown site of infection. Among notified cases, two deaths were reported in unvaccinated people in Queensland.

Conclusions: Although diphtheria remains rare in Australia, 45 cases were notified in the years 2011–2019, compared with one between 1999 and 2010. Robust surveillance remains important to detect all cases. High immunity will need to be maintained across all age groups to prevent outbreaks, and travel and adult booster doses should be encouraged.

4.3 Introduction

Globally, diphtheria incidence declined dramatically following the implementation of vaccination programs in the 1940s, with many industrialised countries having largely eliminated the disease by the 1980s.[1] However, subsequent outbreaks have occurred, the largest in the Newly Independent States of the former Soviet Union in the 1990s, and in Yemen and Bangladesh from 2017.[1-5] Resurgence of diphtheria has been driven by health system disruption and declines in childhood vaccination coverage, often associated with civil unrest and population movement.[1-3, 6, 7]

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*,[6] and very rarely, *Corynebacterium pseudotuberculosis*.[8, 9] The most common clinical presentations are respiratory and cutaneous infection, with subsequent clinical manifestations caused by diphtheria toxin produced by the bacilli.[6] Classic respiratory diphtheria is characterised by a sore throat, fever, swelling of the neck, and a membrane that forms over the back of the throat causing difficulty swallowing and breathing.[10] The toxin can also cause later cardiac and neurological complications.[6] Case fatality rates range from 5% to higher than 20% depending on vaccination status and availability of treatment.[6, 11, 12] Cutaneous diphtheria typically presents as a non-healing ulcerative lesion.[10] Toxin-related complications can occur in cutaneous diphtheria, but are rare due to slow absorption of the toxin from skin lesions.[13] *C. ulcerans* and *C. pseudotuberculosis* are linked to transmission from animals,[14, 15] while *C. diphtheriae* is predominantly spread from human to human by respiratory droplets or direct contact with infected lesions.[6]

Diphtheria vaccines contain diphtheria toxoid (a chemically inactivated form of the toxin), and are highly effective at preventing symptomatic disease.[6] Although they do not prevent colonisation or asymptomatic infection,[6, 15] asymptomatic individuals transmit infection at a reduced rate.[6] Diphtheria vaccines are funded under the Australian National Immunisation Program (NIP) as a 3-dose primary course at 2, 4, and 6 months of age, with booster doses at 18 months, 4 years, and 11–13 years of age, the latter introduced in 2004. The 18-month combination diphtheria-tetanus-pertussis (acellular) (DTPa) booster was removed from the NIP in 2003 and reintroduced in 2016 as part of efforts to improve pertussis control. Doses of adult diphtheria-tetanus-pertussis (acellular) (dTpa) vaccine for parents and carers of newborn babies, to protect them from pertussis (cocoon strategy), were funded by jurisdictions at varying times between 2008 and 2013, replaced by dTpa vaccination for pregnant women, initially funded by jurisdictions from 2014 and then NIP-funded from 2018.[16]

The last detailed review of diphtheria, covering the period from 1991 to 1998, identified 23 notifications for diphtheria in 1991 and 1992 but none between 1993 and 1998.[17] In the most recent decade there have been several changes to the national diphtheria case definition, an increase in the number of notified cases, and the first deaths from diphtheria since 1992.[18] In this epidemiological review we analyse administrative data on diphtheria in Australia from 1999 to 2019.

4.4 Methods

Data sources

Notifications

The Australian National Notifiable Diseases Surveillance System (NNDSS) was established in 1990 and contains data on more than 50 notifiable diseases.[19] Notifications are made to each State or Territory health department, and electronic, de-identified notification data are supplied to the Australian Government Department of Health on a daily basis. For this analysis, included data were NNDSS notifications for confirmed or probable diphtheria, as per the case definition in place at the time (4.7 Appendix A), with an onset date between 1 January 1999 and 31 December 2019. Where the onset date was not available, the earliest of the specimen date, notification date, or notification received date was used. Where site of infection (respiratory or cutaneous) was recorded as unknown in the initial dataset, this was obtained through direct communication with the relevant jurisdiction.

Hospitalisations

Hospitalisation data were obtained from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database (NHMD), which contains line-listed, episode-level records for all hospital admissions in Australian public and private hospitals. Included were any hospitalisations with an admission date between 1 January 2002 and 31 December 2018 (earliest and latest full calendar year of hospitalisation data available) with an International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modifications (ICD-10-AM) principal or additional diagnosis code for diphtheria (A36.0 [pharyngeal diphtheria], A36.1 [nasopharyngeal diphtheria], A36.2 [laryngeal diphtheria], A36.3 [cutaneous diphtheria], A36.8 [other diphtheria], 36.9 [diphtheria, unspecified]). Length of stay was capped at 30 days in the dataset provided by AIHW, so hospitalisations reported with a 30-day length of stay may represent longer hospitalisations. Admission year was not supplied by AIHW where length of stay was greater than 30 days. Where admission year was not available, separation year was used. Counts <5 are

expressed as a range to comply with the data release condition that small counts be suppressed in published reports.

Mortality

Mortality data were obtained from the Australian Coordinating Registry (ACR) for deaths from 2006 onwards, and from the Australian Bureau of Statistics (ABS) for deaths prior to 2006. Data included were deaths with diphtheria recorded as an underlying or associated cause (only underlying cause available for ABS data), defined using the ICD-10 code A36, from 1 January 2003 (earliest full calendar year of data available) to 31 December 2019. Counts <6 are expressed as a range to comply with the data release condition that small counts be suppressed in published reports. Deaths were also identified from the 'separation mode' field within the NHMD hospitalisation dataset, and from the 'died' field in the NNDSS.

Population estimates

Mid-year Australian resident population estimates by age and jurisdiction were obtained from the ABS. Aboriginal and Torres Strait Islander population estimates for 2001 to 2019 were taken from the back cast and projected estimates as provided by the ABS based on the 2016 census. Aboriginal and Torres Strait Islander population estimates for 1999 and 2000 were derived by calculating the average age-specific annual increase in population for the years 2001 to 2006 and deducting this from the 2001 estimated population to provide a 2000 estimate, and then from the 2000 estimate to provide a 1999 estimate.

Data analyses

Data were analysed descriptively, including proportions and rates. Variables analysed from the NNDSS dataset included: confirmation status (confirmed/probable), age at onset, sex, Aboriginal and Torres Strait Islander status, year of diagnosis, whether died of the disease, vaccination status, state/territory, and place of acquisition. All variables were assessed for data completeness. The following derived variables were created: age group from onset age, and overseas/local acquisition from place of acquisition.

Variables analysed from the AIHW hospitalisation dataset included: age, sex, Aboriginal and Torres Strait Islander status, state of residence, admission year, length of stay, separation mode, and principal and additional diagnosis fields. ICD-10-AM codes A36.0, A36.1, and A36.2 were combined

for analysis as respiratory diphtheria, and A36.8 and A36.9 were combined as unknown diphtheria (unspecified site).

Rates were calculated using mid-year ABS population data, or jurisdiction or age-specific ABS population estimates, or Aboriginal and Torres Strait Islander population projections as appropriate, and presented per 100,000 population per year. Summary statistics, including median and interquartile range (IQR), were calculated for age and length of stay.

Analysis was performed using Microsoft Excel 2010 and Stata 14.2 (Statacorp LLC, College Station, TX, USA).

Ethics

This epidemiological review was approved by the Australian Capital Territory (ACT) Human Research Ethics Committee (HREC) (2019/ETH12123) and the Australian National University HREC (2020/162).

4.5 Results

Notifications

Secular trends

A total of 46 notifications for diphtheria were recorded between 1999 and 2019. Of these, 38 (83%) were cutaneous diphtheria and eight (17%) were respiratory diphtheria. Forty-five (98%) of the cases were reported from 2011 onwards, with only one notification of cutaneous diphtheria (2001) between 1999 and 2010 (Figure 4.1). The average annual notification rate was 0.008 per 100,000 population per year for cutaneous diphtheria and 0.002 per 100,000 population per year for respiratory diphtheria. The rate was higher in the second half of the study period (2010 to 2019): 0.016 per 100,000 per year for cutaneous diphtheria, and 0.003 per 100,000 per year for respiratory diphtheria.

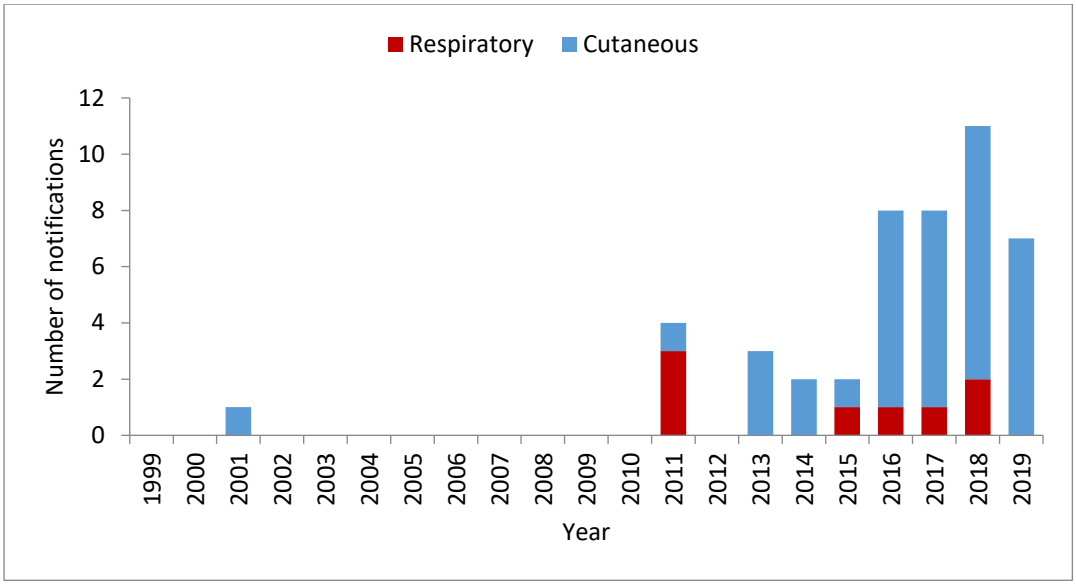

Figure 4.1. Number of notifications of cutaneous and respiratory diphtheria, 1999–2019, Australia

Data source: National Notifiable Diseases Surveillance System

Age and sex

The median age among the eight notified cases of respiratory diphtheria was 31.5 years (range 21–85 years; IQR 22.75–50.25) and for the 38 cases of cutaneous diphtheria was 52.5 years (range 6–83 years; IQR 25.25–60.0). The highest rate of notifications for respiratory diphtheria was in the 15–24 year age group, and the highest rate for cutaneous diphtheria was in the ≥65 age group, followed by the 50–64 year and 15–24 year age groups (Figure 4.2). Females were overrepresented among notified cases of respiratory diphtheria (n=6, 75%) and males among notified cutaneous diphtheria (n=27, 71%).

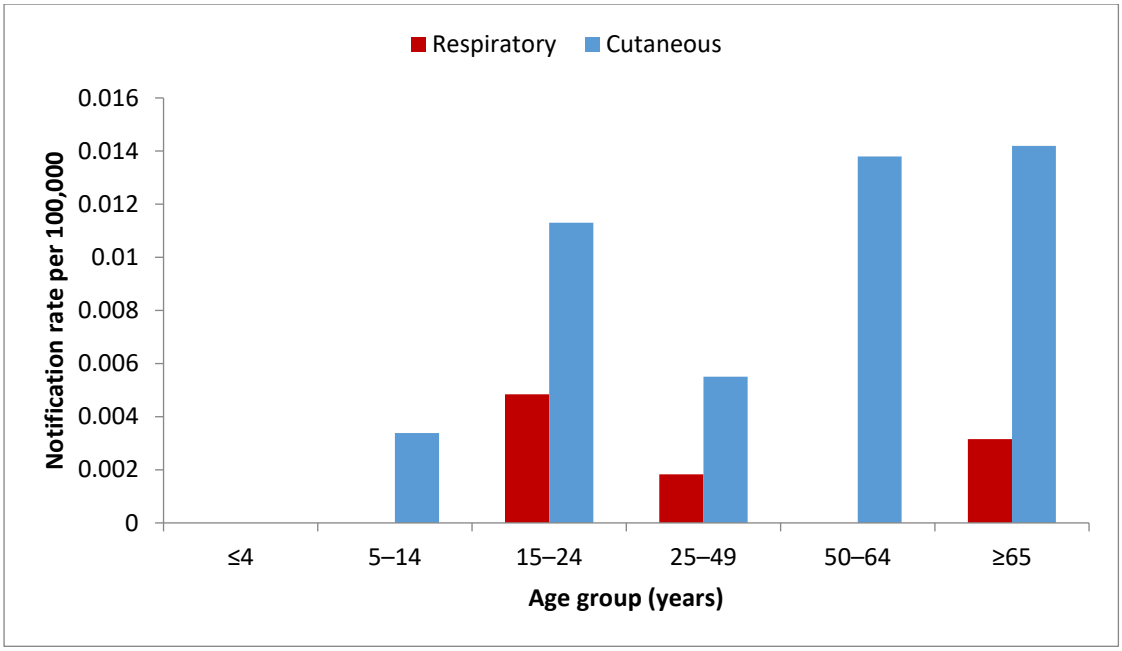

Figure 4.2. Rate (per 100,000 per year) of respiratory and cutaneous diphtheria notifications by age group, Australia, 1999–2019

Data source: National Notifiable Diseases Surveillance System

Organism

C. diphtheriae accounted for most notifications (40 cases; 87%). The first *C. ulcerans* case was notified in 2013, with three of the six total *C. ulcerans* notifications in 2018. Of the 40 *C. diphtheriae* notifications, six (15%) were respiratory and 34 (85%) cutaneous infections, and of six *C. ulcerans* cases, two (33%) were respiratory and four (67%) cutaneous.

Place of acquisition

The Northern Territory had the highest rate of cutaneous notifications (n=2, 0.043 per 100,000 population per year), followed by Queensland (n=26, 0.029 per 100,000 per year) (Table 4.1). Queensland accounted for 6/8 (75%) respiratory notifications (0.007 per 100,000 per year), with one in each of New South Wales and Victoria; 3/8 (38%) were acquired overseas and 4/5 (80%) locally acquired cases occurred in Queensland. The average annual rate for Queensland and the Northern Territory combined was approximately ten times higher than the rate for the other jurisdictions combined, in both the full study period (1999–2019; 0.03 per 100,000 per year compared to 0.003 per 100,000 per year) and the second half (2010–2019; 0.054 per 100,000 per year compared to 0.005 per 100,000 per year). Of 38 cutaneous diphtheria notifications, infection was acquired overseas in 27 (71%), locally in seven (18%), and unknown in four (11%). All seven local acquisitions and 18/27 (67%) overseas acquisitions were from Queensland, with 12 between 2013 and 2016. Of

cases acquired in Australia, we were unable to identify which may have been import-linked. Of the 30 notifications where infection was acquired overseas, 21 (70%) were acquired in the Western Pacific Region and nine (30%) in the South East Asia Region. Of the 18 overseas-acquired cutaneous cases in Queensland, countries of acquisition included Papua New Guinea (n=4), Solomon Islands (n=6), Cambodia (n=1), Philippines (n=2), Sri Lanka (n=1), New Zealand (n=1), and Vanuatu (n=3).

Table 4.1. Number and rate per 100,000 population per year of notified diphtheria cases by site of infection, place of acquisition, and reporting jurisdiction, Australia, 1999–2019

Notifying jurisdiction*	Respiratory diphtheria					Cutaneous diphtheria					
	Place of acquisition			N	rate	Place of acquisition				n	rate
	Overseas		Local			Overseas		Local	Unknown		
	WPR**	SEAR†				WPR*	SEAR†				
Queensland	1	1	4	6	0.007	17	1	7	1	26	0.029
New South Wales	0	0	1	1	0.001	2	0	0	2	4	0.003
Victoria	0	1	0	1	0.001	0	2	0	1	3	0.003
South Australia	0	0	0	0	—	1	1	0	0	2	0.006
Northern Territory	0	0	0	0	—	0	2	0	0	2	0.043
Western Australia	0	0	0	0	—	0	1	0	0	1	0.002
Total	**1**	**2**	**5**	**8**	**0.002**	**20**	**7**	**7**	**4**	**38**	**0.008**

*No cases were reported in the Australian Capital Territory or Tasmania

**WPR: Western Pacific Region

† SEAR: South East Asia Region

Data source: National Notifiable Diseases Surveillance System

Aboriginal and Torres Strait Islander status

Of the eight respiratory diphtheria notifications, one (13%) was reported to be in an Aboriginal and Torres Strait Islander person (in Queensland), six (75%) in non-Indigenous people, with one not recorded. Of 38 cutaneous diphtheria notifications, three (8%) were reported to be in Aboriginal and Torres Strait Islander people (two in Queensland and one in Victoria), 32 (84%) non-Indigenous people, and three not recorded. The rate of respiratory and cutaneous notifications in Aboriginal and

Torres Strait Islander people was 0.007 (3.9 times higher than the overall population rate) and 0.021 per 100,000 per year (2.5 times higher than the overall population rate), respectively.

Vaccination status

Among the 4/8 respiratory notifications with a recorded vaccination history, one had 4 doses recorded, one had one dose recorded, and two were unvaccinated, both of whom died of the disease. Among 25 cutaneous notifications with a known vaccination history, five (20%) were unvaccinated and 20 had recorded doses (five with 4–5 doses, 15 with 1–2 doses). All six cases (any site of infection) reported as having 4 or 5 previous doses of diphtheria-containing vaccine were younger than 25 years of age.

Hospitalisations

From 2002–2018, 327 hospitalisations had diphtheria listed as a diagnosis but only 29 (9%; 0.008 per 100,000 per year) had diphtheria recorded as the principal diagnosis. Of these 29, 8 (28%; 0.002 per 100,000 per year) were respiratory, 8 (28%; 0.002 per 100,000 per year) were cutaneous, and 13 (45%; 0.003 per 100,000 per year) were unknown. The median length of stay for diphtheria (principal diagnosis) was 3 days (IQR 1–6: respiratory 2 days [IQR 1.8–4), cutaneous 4 days [IQR 2.5–5.25]). Of the 29 principal diagnosis hospitalisations, 13 (45%) occurred in years with no notifications, including all three hospitalisations from the Northern Territory.

Of the 298 hospitalisations with diphtheria as an additional diagnosis, 133 (45%) were in the Northern Territory, and 198 (66%) were cutaneous. Common principal diagnoses among these 298 hospitalisations included endocarditis (n=25) and skin infection-related codes, such as cellulitis, ulcers, and wound infections (n=50).

Mortality

There were 1–5 deaths recorded in the ACR causes of death data with diphtheria as the underlying or an associated cause of death between 2006 and 2019, and no related deaths recorded in the ABS data between 2003 and 2005. There were 5 deaths recorded in hospitalisations coded as due to diphtheria (one principal and four additional diagnosis) in the AIHW data, and 2 deaths recorded in notified cases in the NNDSS. These individuals may overlap across datasets.

The two deaths reported in the NNDSS both occurred in Queensland and were acquired in Australia; both were in the 20–29 years age group and were unvaccinated.

4.6 Discussion

Both respiratory and cutaneous diphtheria remain rare in Australia, with an average annual incidence of notified cases of 0.002 per 100,000 population per year for respiratory diphtheria and 0.008 per 100,000 population per year for cutaneous diphtheria from 1999 to 2019. In the last detailed review of diphtheria, there were no cases reported between 1993 and 1998.[17] In this review, there was one case reported in the NNDSS between 1999 and 2010, with 37 cutaneous cases and 8 respiratory cases occurring since 2011, and two deaths. Both deaths reported in the NNDSS were in unvaccinated young adults in Queensland who acquired infection locally, with the 2011 death being in a close contact of a partially vaccinated case who acquired infection in Papua New Guinea,[20] while the source of infection for the 2018 death has not been documented. Notification rates in Aboriginal and Torres Strait Islander peoples, although 2–4 times higher than the overall population, were low.

Both cutaneous and respiratory diphtheria occurred mostly among adults in Australia, with no cases of respiratory diphtheria reported in children aged <15 years between 1999 and 2019. This absence of respiratory cases in children reflects the high coverage achieved by the childhood immunisation program in Australia. This is particularly evident over the last two decades, with coverage (4 doses of DTPa at 24 months of age) above 90% since 2000.[21, 22] This shift in respiratory diphtheria epidemiology away from childhood was already present in the previous review period (1991–1998)[17] and is consistent with findings in other high-coverage countries.[3, 23, 24] Both the 1997/98 and 2007 Australian national serosurveys found high immunity in children, decreasing to approximately 60% in adults aged 50 years or older, suggesting that almost half of older adults may be susceptible to diphtheria.[25, 26] The occurrence of respiratory diphtheria predominantly in adults over our study period is likely due to a combination of waning post-vaccination immunity in adulthood[6, 27,25, 26] and lower historical childhood immunisation coverage, which was estimated at 59–75% in the 1970s and 1980s.[28, 29] A single booster dose of diphtheria-containing vaccine is recommended for adults at 50 years of age (introduced in 2000, replacing previous recommendation for a booster dose every 10 years) and again at 65 years of age. If travelling overseas, a booster is recommended if more than 10 years has passed since the most recent dose (or five years for high-risk travel), introduced in 2013 to address concerns about waning immunity.[16, 27] Ascertaining diphtheria immunisation status pre-travel remains important, with the majority of cutaneous cases and a third of respiratory cases acquired overseas.

Queensland reported the highest rate of respiratory notifications and the second highest rate of cutaneous notifications. As cutaneous diphtheria occurs mostly in the tropics,[30, 31] the Queensland

climate may contribute, with all seven local acquisitions of cutaneous diphtheria over the study period occurring in Queensland. Other reasons for higher numbers in Queensland may include travel patterns and better ascertainment of cases through clinical diagnosis and more complete notification. Due to changes to the national surveillance case definition, cutaneous diphtheria cases were not required to be notified to NNDSS from 2013 to 2016. However, Queensland did not incorporate these changes in its local case definition, notifying 12 cutaneous cases over this period. Although the Northern Territory reported the highest rate of cutaneous notifications, this corresponds to only two cases. The Northern Territory also recorded the highest rate of hospitalisations during the study period. As the diphtheria ICD codes do not distinguish between toxigenic and non-toxigenic disease this is likely a reflection of the burden of non-toxigenic diphtheria, which remains endemic in Central Australia.[32] Non-toxigenic diphtheria, while not notifiable in Australia, is emerging as a cause of substantial infections internationally, including persistent sore throats, endocarditis, septic arthritis, and cutaneous infections.[33, 34] Non-toxigenic strains can acquire the toxin gene if lysogenised by a bacteriophage.[15]

Vaccination status was unknown for half of respiratory notifications. Among those with a known vaccination status (n=4) two cases were unvaccinated and died of the disease. Of the two-thirds of cutaneous cases with known vaccination status, the proportion that had received at least 4 doses and the proportion unvaccinated were the same (one-fifth), reflecting the limited effectiveness of vaccination in preventing wound colonisation. Wounds are also often co-infected with other pathogens, such as *Staphylococcus aureus*, so it may be unclear whether *Corynebacterium* detected is the causative organism or only commensal.[13, 30, 35] Nevertheless, similar to respiratory cases, appropriate prophylactic antibiotics remain important for contacts of cutaneous cases, along with catch-up vaccination if required, to prevent transmission.

Similarly to Australia, increases in diphtheria cases have been documented in Belgium since 2010,[35] and in the UK since 2015.[14] Internationally *C. ulcerans* is playing an increasing role in the burden of diphtheria in highly vaccinated populations,[8, 9, 12, 36] becoming the dominant organism in the UK since the 1990s due to locally acquired *C. ulcerans* cases associated with exposure to domestic animals.[12, 14] In Australia, *C. diphtheriae* still accounted for 85% of notified cases from 1999 to 2019. *C. ulcerans* was added to Australia's case definition in 2004, but no cases were notified until 2013. Vaccination appears to be effective against *C. ulcerans* toxin, however concerns have been raised that the greater diversification of the toxin gene in *C. ulcerans* compared to *C. diphtheriae* could lead to decreased effectiveness of the vaccine over time.[37] *C. pseudotuberculosis* has been made notifiable in some European countries to better characterise disease caused by this organism.[8, 9]

While there have been several changes to the Australian surveillance case definition between 1999 and 2019, there were few cases during the period with the broadest case definition (2004 to 2012). During this time, two out of the three notified respiratory cases were asymptomatic carriers[18, 38, 39] with the national case definition changed in 2013 to require the presence of clinical symptoms. This suggests the minor re-emergence of respiratory notifications in the years following was unlikely to be due to case definition changes. The increased number of notified cases seen since 2011 largely comprised cutaneous cases. Although cutaneous diphtheria was notifiable from 2004 to 2012, it is unclear to what extent cases were routinely notified. The case definition was changed in 2017 to specifically include cutaneous presentations which may have encouraged notification and account for some of the increase in cutaneous cases since 2011.

There are several limitations to this study. Notification data are generally not considered to be representative of all cases in the population, but the sensitivity of notification datasets may be better for rare and serious conditions such as respiratory diphtheria. Notification data were incomplete for a number of fields, including Aboriginal and Torres Strait Islander status and vaccination status, and recorded vaccinations in notified cases may not reflect complete vaccination history, particularly for vaccinations received prior to the introduction of the Australian Childhood Immunisation Register in 1996. The number of hospitalisations for diphtheria is disproportionately high compared to the number of notifications. This is likely due to a lack of specificity in diphtheria ICD-10-AM codes and may also be due, in part, to errors in coding, which are more common for rare diseases.[40] Additionally, hospitalisation data are episode-level records and may include multiple records for individual cases transferred between hospitals or readmitted. This, in combination with a large proportion of hospitalisations with an unknown site of infection, limited our ability to describe severe disease due to toxigenic respiratory and cutaneous diphtheria. There were also discrepancies in the numbers and details of deaths across datasets.

In summary, despite an increase in cases over the past decade, diphtheria remains rare in Australia. It is however important to maintain high levels of vaccination coverage. In particular, pre-travel booster vaccination should continue to be encouraged, in line with recommendations in the Australian Immunisation Handbook.[27]

4.7 Appendix

Appendix A. Changes to the diphtheria national surveillance case definition

Year	Case definition	Main changes
1991[41]	Isolation of toxigenic *C. diphtheriae* and one of the following: pharyngitis and/or laryngitis (with or without membrane), OR toxic (cardiac or neurological) symptoms	N/A Cutaneous diphtheria notifiable only with toxic symptoms.
2004[41]	Confirmed Case Isolation of toxigenic *C. diphtheriae* or toxigenic *C. ulcerans*. Probable Case Isolation of *C. diphtheriae* or *C. ulcerans* (toxin production unknown) and one of the following presentations as clinical evidence: pharyngitis and/or laryngitis (with or without membrane) *or* toxic (cardiac or neurological) symptoms OR Clinical evidence as above and an epidemiological link to a confirmed case	Inclusion of *C. ulcerans* in confirmed case definition. Does not require clinical evidence/symptoms to be a confirmed case. Inclusion of a probable case definition. Cutaneous diphtheria notifiable.
2013[42]	Confirmed Case Isolation of toxigenic *C. diphtheriae* or toxigenic *C. ulcerans* AND clinical evidence Probable Case Isolation of *C. diphtheriae* or *C. ulcerans* (toxin production unknown) and clinical evidence OR Clinical evidence and an epidemiological link to a confirmed case Clinical evidence: pharyngitis and/or laryngitis (with or without membrane) *or* toxic (cardiac or neurological) symptoms	Requires clinical evidence to be a confirmed case. Cutaneous diphtheria notifiable only with toxic symptoms.
2017[43]	Confirmed case Isolation of toxigenic *C. diphtheriae* or toxigenic *C. ulcerans* from upper respiratory tract infection OR Skin lesion Probable case Isolation of *C. diphtheriae* or *C. ulcerans* from a respiratory tract specimen (toxin production unknown) AND Upper respiratory tract infection with an adherent membrane of the nose, pharynx, tonsils or larynx OR Upper respiratory tract infection with an adherent membrane of the nose, pharynx, tonsils or larynx AND Epidemiological link to a confirmed case	Specific inclusion of skin lesion in confirmed case definition. Cutaneous diphtheria notifiable.

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Chapter 6

Teaching

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6.1 Background

Teaching and mentoring is a core competency of field epidemiology training programs internationally. The MAE includes two teaching requirements: a lessons from the field (LFF) delivered as a case study to our cohort peers on a topic of our choosing, and as a cohort deliver a day of teaching to the proceeding cohort during the third course block. I chose to focus my contribution to both teaching sessions on vaccine-related concepts, as I felt this was a skill set to which my peers at other placements were likely not exposed.

6.2 Teaching activities

Lessons from the field

My LFF was a case study on vaccination coverage estimates, the use of the Australian Immunisation Register as a data source, and the use of birth cohorts in coverage estimates and notification analysis. I chose this topic as this was something I was learning about as I was developing a protocol for my epidemiological study on measles (I had also included coverage estimates in the protocol, which did not eventuate in the project). Acknowledging that my peers were time-poor, the case study consisted of only essential background information, with links provided to more detail if desired or required and was mostly driven by a series of questions. I opted to make some of the questions in the case study discussion points for the zoom session, rather than requesting that they be completed ahead of time. I presented this LFF in May 2021.

The learning objectives were to:

1. Describe different methodologies for estimating vaccination coverage and their advantages and disadvantages
2. Determine birth cohorts for calculating vaccination coverage based on the National Immunisation Program schedule
3. Describe how milestone assessment age and delayed vaccination impact on coverage estimates
4. Select appropriate birth cohorts for describing vaccine-preventable disease cases based on historical changes to the National Immunisation Program schedule

Teaching to the MAE21 cohort

For this session, I worked with fellow MAE20 Luke Le Grand on a didactic session on vaccine development and safety, with the safety aspect being my contribution. The teaching was planned for April 2021, at a time when the COVID-19 vaccination rollout was beginning, and vaccine safety was in the spotlight. My contribution to the session covered how vaccines are monitored post-licensure, including passive surveillance through the Therapeutic Goods Administration (TGA), and active surveillance through AusVaxSafety, as well as how safety signals are detected and investigated. I thought that most MAE scholars would likely interact with the vaccine rollout in their field placements, and as adverse event reporting involves jurisdictional health departments, many would likely benefit from an understanding of how the system works.

I tried to match the level of detail provided to the time allocation, to avoid it being too rushed. There were opportunities to discuss students' thoughts about signal investigation in the presentation to try to improve engagement.

The learning objectives for the part of the session that I presented were:

1. Describe the role of the TGA in vaccine pharmacovigilance
2. Define Adverse Events Following Immunisation (AEFIs) and Adverse Events of Special Interest (AESIs) and discuss how they are investigated
3. Describe the role of active surveillance in vaccine pharmacovigilance

The session was evaluated via a survey. There were 18 respondents, 17 of whom either agreed or strongly agreed that the session was well organised and prepared, there were learning objectives presented, the content was relevant, they were motivated to learn more about the subject, there were opportunities to ask questions and participate in discussion, the learning objectives were met, and they were satisfied with the session. One area in which we could have been improved was interactivity. Of the 18 survey respondents, 16 agreed that the teaching methods and aids were appropriate, with one respondent commenting that they would have liked more interaction. This can be challenging over Zoom, and with short time allocations per session, but we could have made more use of the tools available, such as breakout rooms and polls. The same survey respondent commented that more time should have been allocated per session by running it over two days.

Other teaching activities

In addition to the core teaching requirements for the MAE, I also participated in training conducted by NCIRS. NCIRS runs a weeklong module of a clinical science subject for third year University of

Sydney Applied Medical Science students, which includes online lectures and a workshop. The workshop is a case study of influenza, including programmatic considerations and the 2011 investigation of reports of febrile seizures in children following influenza vaccine administration. The tutorial, moved to an online format in 2020 due to COVID-19, included breakout room tutorial sessions, one of which I led with support from Dr Quinn.

NCIRS also conducts a subject called Vaccines in Public Health for the University of Sydney Master of Public Health degree. One of the teaching sessions is the Texarkana case study: a commonly used public health case study of a real-life outbreak of measles in the USA in the 1970s. The case study offers students an opportunity to understand how outbreaks of vaccine preventable diseases may be investigated and includes a section on calculating vaccine effectiveness. I independently led a group of six students through the case study in August 2021 and provided a recorded version to be uploaded for students.

6.3 Lessons learnt

The pandemic presented challenges for all of our teaching activities. The MAE21 teaching day was originally planned to be delivered in-person in Canberra but was moved online due to issues around state border closures and ability to travel. This not only changed the format of delivery at short notice, but also shortened the time available in the day, due to time-zone differences for scholars. It required us to be flexible and organised as a cohort.

Similarly, student engagement over Zoom is more difficult than in the classroom. Sessions take longer due to the need to allow long pauses for students to unmute and contribute. Consideration must be given to student engagement for any teaching sessions, but this is particularly true when teaching occurs online, and presenters should make full use of opportunities for interaction.

The COVID-19 pandemic increased placement workload for scholars, who were often working in pandemic response activities in addition to their MAE projects, limiting our available time. Teaching activities should be tailored and appropriate for the audience, accounting for these circumstances, so that participants can maximise their learning.

6.4 Acknowledgements

All supervisors, particularly Dr Pourmarzi and Dr Quinn, supervised the development of teaching materials, and Dr Dey and Dr Quinn invited me to participate in the additional teaching activities.