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Paediatric Active Enhanced Disease Surveillance (PAEDS) 2019: Prospective hospital-based surveillance for serious paediatric conditions

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Abstract

Introduction

The Paediatric Active Enhanced Disease Surveillance (PAEDS) network is an Australian hospital-based active surveillance system employing prospective case ascertainment for selected serious childhood conditions, particularly vaccine preventable diseases and potential adverse events following immunisation (AEFI). This report presents surveillance data for 2019.

Methods

Specialist nurses screened hospital admissions, emergency department records, laboratory and other data on a daily basis in seven paediatric tertiary referral hospitals across Australia, to identify children with the conditions under surveillance. Standardised protocols and case definitions were used across all sites. In 2019, the conditions under surveillance comprised: acute flaccid paralysis (AFP; a syndrome associated with poliovirus infection), acute childhood encephalitis (ACE), influenza, intussusception (IS; a potential AEFI with rotavirus vaccines), pertussis, varicella-zoster virus infection (varicella and herpes zoster), invasive meningococcal and invasive Group A streptococcus diseases and two new conditions, Kawasaki disease and gram-negative bloodstream infections. An additional social research component continued to evaluate parental attitudes to influenza vaccination.

Results

PAEDS captured 2,701 cases for 2019 across all conditions under surveillance. Key outcomes of PAEDS included: contribution to national AFP surveillance to reach the World Health Organization reporting targets for detection of poliomyelitis cases; demonstration of high influenza activity in 2019 and influenza-associated deaths in ACE cases; identification of key barriers to influenza vaccination of children hospitalised for acute respiratory illness; reporting of all IS cases associated with vaccine receipt to relevant state health department; and showing a further reduction nationally in varicella cases. Enhanced pertussis surveillance continued to capture controls to support vaccine efficacy estimation. Invasive meningococcal disease surveillance showed predominance of serotype B and a reduction in cases nationally. Surveillance for invasive group A streptococcus captured severe cases in children. Monitoring of Kawasaki disease incidence and gram-negative bloodstream infections commenced.

Conclusions

PAEDS continues to provide unique policy-relevant data on serious paediatric conditions using sentinel hospital-based enhanced surveillance.

Keywords: paediatric, surveillance, child, hospital, vaccine preventable diseases, adverse event following immunisation, acute flaccid paralysis, encephalitis, influenza, intussusception, pertussis, varicella zoster virus, meningococcal, group A streptococcus, Kawasaki, bloodstream infections.

Introduction

This is the fifth annual report of the Paediatric Active Enhanced Disease Surveillance (PAEDS) network and summarises data collected in 2019. PAEDS data, including their impact and outcomes from previous years, can be found in earlier reports.¹⁻⁴

PAEDS is a sentinel hospital-based active surveillance system for serious childhood conditions of public health importance, particularly vaccine preventable diseases (VPDs) and adverse events following immunisation (AEFI). Through prospective case identification and ascertainment, PAEDS collects timely and detailed enhanced clinical data on children requiring hospitalisation for the select conditions under surveillance. In some instances, emergency department (ED) and other ambulatory care presentations are also included. Data captured by PAEDS are used to better understand these conditions; to inform policy and practice under the National Immunisation Program (NIP); and to enable rapid public health responses for certain conditions of public health importance. PAEDS is better positioned to adequately capture timely and comprehensive data than other surveillance systems that are usually unable to do so.^{5,6}

During 2019, the PAEDS network consisted of seven participating hospitals:

- The Children's Hospital at Westmead (CHW), Sydney, New South Wales (NSW);
- The Royal Children's Hospital (RCH), Melbourne, Victoria;

- Women's and Children's Hospital (WCH), Adelaide, South Australia;
- Perth Children's Hospital (PCH), Perth, Western Australia;
- Queensland Children's Hospital (QCH), Brisbane, Queensland;
- Royal Darwin Hospital (RDH), Darwin, Northern Territory; and
- Monash Health, Melbourne, Victoria.

All sites remained active with PAEDS in 2019. In 2019, one non-PAEDS site, Sydney Children's Hospital Randwick (SCH), contributed data into the network database for a grant funded study of gram-negative bloodstream infections. PAEDS is coordinated by the National Centre for Immunisation Research and Surveillance (NCIRS) based at CHW in Sydney.

PAEDS activities are substantially supported through funding from the Australian Government Department of Health and the six respective state and territory health departments as well as external research grants. In addition, the Australian Paediatric Surveillance Unit (APSU) and the Influenza Complications Alert Network (FluCAN) collaborate with PAEDS on specific conditions. PAEDS produces monthly data reports for all funding bodies and collaborators, including timely notification of severe cases. Core seasonal influenza data are reported through FluCAN, with some sites producing additional weekly or ad-hoc reports for their local health authorities.

Methods

Active case ascertainment

Specialist surveillance nurses in each participating hospital identified children diagnosed with the conditions under surveillance, as defined in Table 1, by reviewing admission and ED databases, clinical records, laboratory logs and through liaison with clinical and laboratory staff.¹⁻⁴

In 2019, PAEDS participating hospitals were approved to operate under a waiver-of-consent model for surveillance of approved conditions. Previously, PAEDS sites were approved by individual site ethics committees. Leading up to 2019, PAEDS successfully transitioned to a new ethics framework (Figure 1), approved by the Sydney Children's Hospital's Network (SCHN) Human Research Ethics Committee (HREC/18/SCHN/72). Six sites participated in ethics approval via the National Mutual Acceptance scheme and were approved under the PAEDS Program of Research; RDH was approved by the Northern Territory Department of Health and Menzies School of Health Research (2017-2775). The PAEDS Program was designed to clearly distinguish between surveillance activities that operate under a waiver of consent, and linked research activities that require consent. This approach has led to streamlined ethics and governance processes and improved the transparency of all activities undertaken within the network. The social research was also approved under the National Mutual Acceptance (NMA) Scheme by the SCHN Human Research Ethics Committee (HREC/18/SCHN/207) and the Northern Territory Department of Health and Menzies School of Health Research (2017-2775). The additional site (SCH, Randwick) was approved by SCHN HREC to participate in GNBSI surveillance only.

Surveillance nurses collected detailed clinical information from the medical records and vaccination history from the Australian Immunisation Register (AIR). Information not available in the medical record was obtained

by contacting the child's parent/guardian; participation was voluntary. In some cases, the parent/guardian was approached for consent to their child's participation in additional research studies, involving elements such as long-term follow-up or non-routine specimen collection. In this instance, a patient information sheet and consent form was provided to facilitate participation (Figure 2).

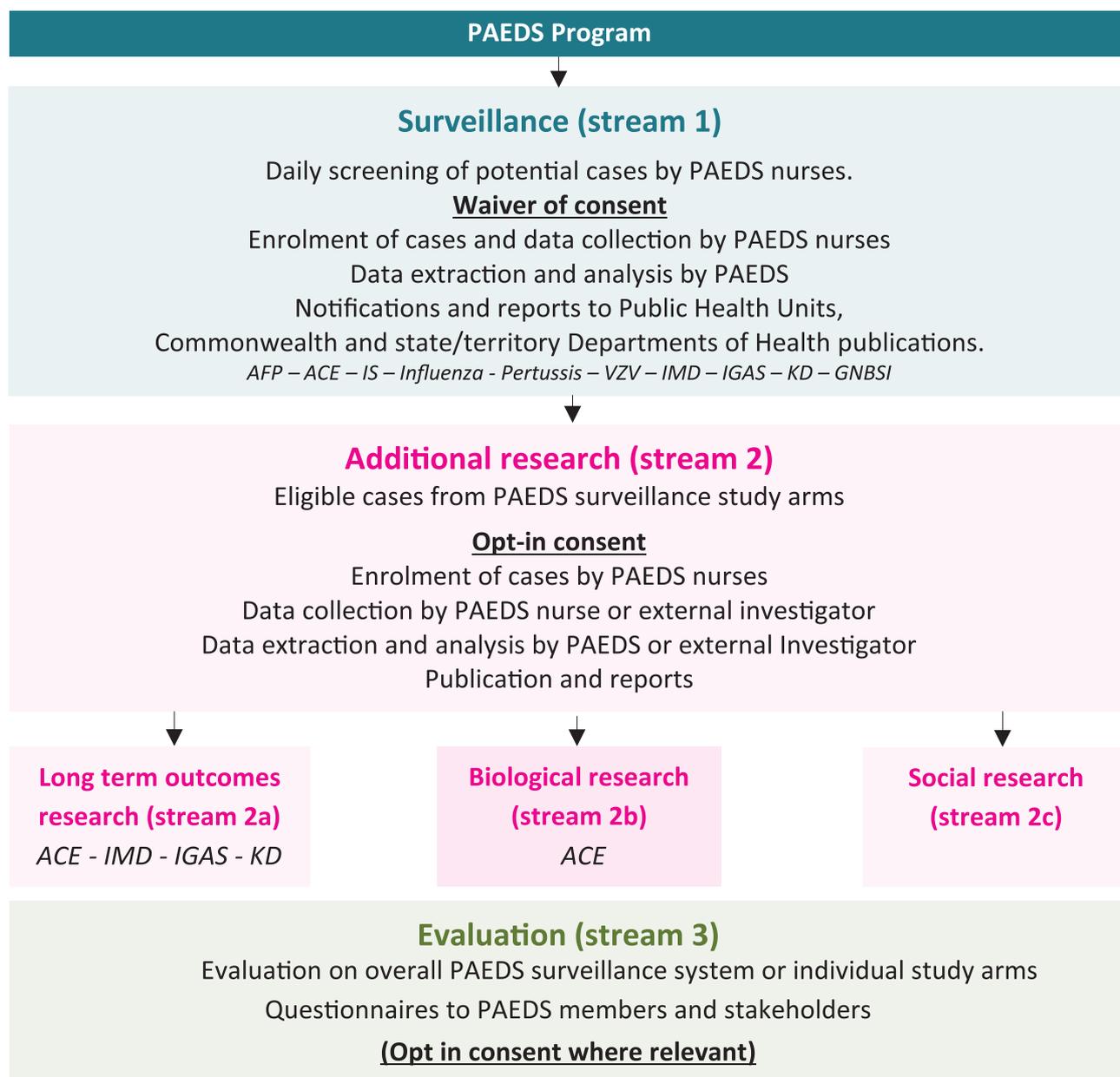
Conditions under surveillance

In 2019, there were ten conditions approved for surveillance: acute flaccid paralysis (AFP), acute childhood encephalitis (ACE), intussusception (IS), pertussis, varicella-zoster virus infection (VZV; varicella and herpes zoster), influenza (in collaboration with FluCAN), invasive meningococcal disease (IMD), invasive group A streptococcus (IGAS) and two new conditions, Kawasaki disease (KD) and gram-negative bloodstream infections (GNBSI). All sites suspended IS surveillance in July 2019 following discussion with stakeholders. Surveillance of AFP, influenza and KD was conducted by all sites; ACE was expanded from five to seven sites with RDH and MH commencing surveillance in July 2019. A social research component of influenza continued in CHW, WCH, PCH, QCH and RDH. In response to funding adjustments, site participation in each condition varied from July 2019 (Table 2).

Collection of biological samples

Surveillance nurses facilitated collection of samples in line with public health requirements and condition protocols. For example, children hospitalised with AFP require collection of two stool samples for enteric virus identification by the National Enterovirus Reference Laboratory (NERL) in Melbourne, Australia as part of the Global Polio Eradication Initiative.^{7,8} For other conditions, samples were collected for planned viral genotyping (e.g. VZV) or for additional pathogen characterisation (e.g. ACE, IGAS, GNBSI).

Figure 1. PAEDS Program Structure

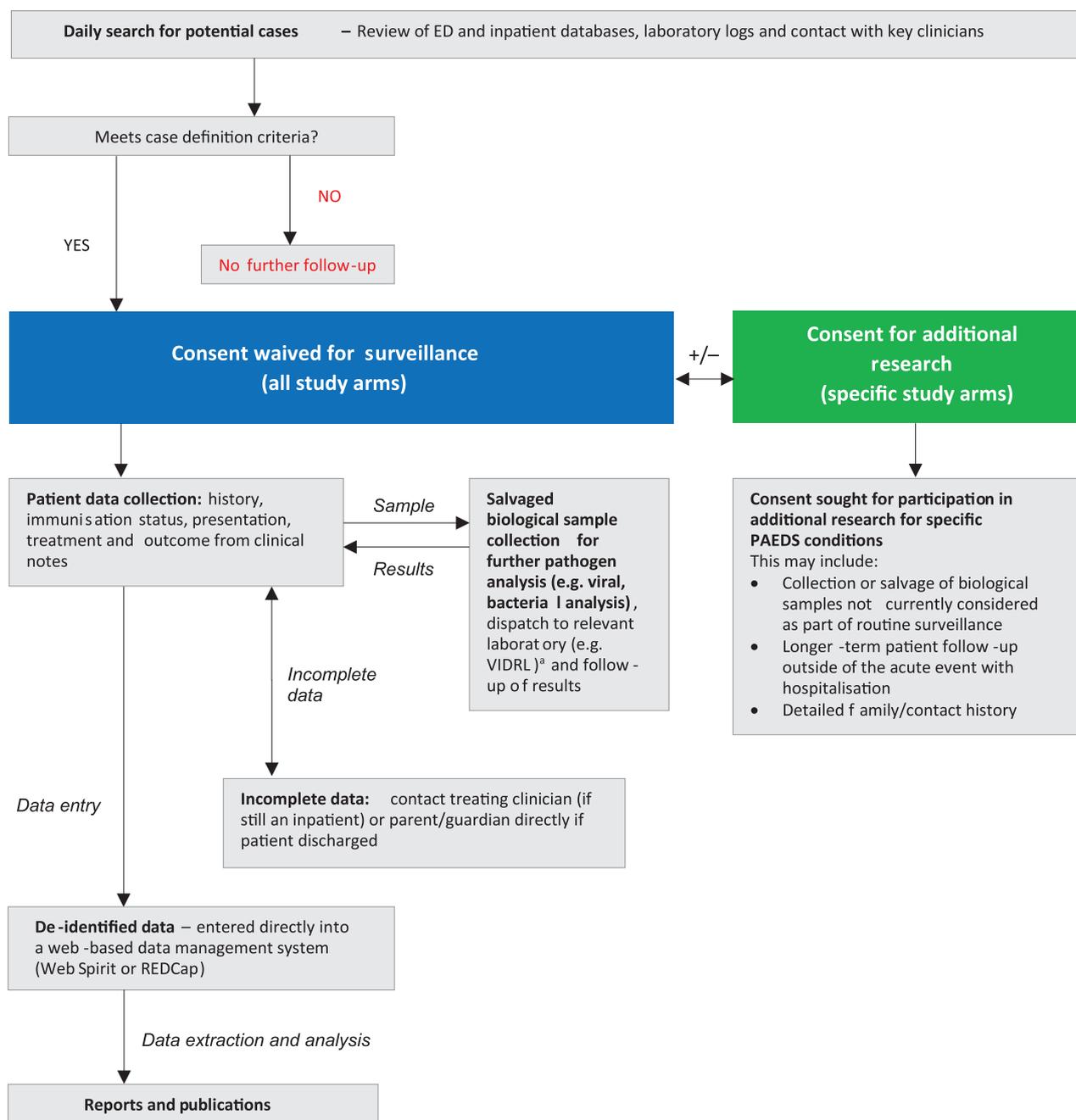


Quality assurance and ICD-10-AM audits

In previous years, PAEDS nurses at each site conducted regular retrospective audits of hospitalisation records to check for completeness of case ascertainment and for the purpose of case recapture.¹⁻⁴ This was conducted by searching for primary and secondary ICD-10-AM codes ascribed to the relevant conditions (e.g. K56.1 for IS). Cases ascertained through these audits were compared with the cases ascertained prospectively by PAEDS for the same period.

Additional cases identified by the ICD-10-AM audit process were retrospectively included into PAEDS. Previous ICD-10-AM audits resulted in consistently low additional case numbers, with only 4–5% of total recruited cases for 2017–2018 captured from ICD-10-AM audits.¹⁻⁴ The audit framework was modified by PAEDS from July 2019 such that audits were completed for new conditions only, or if a specific need for quality assurance purposes was identified. For example, due to an identified decrease in AFP case numbers in South Australia (< 1 non-polio AFP case

Figure 2: PAEDS method for surveillance using the waiver of consent model plus opt-in consent for additional research of specific study arms



per 100,000 children aged < 15 years) identified by the Commonwealth Polio Expert Panel, WCH conducted an ICD-10-AM audit for the period of July to December 2019 which confirmed no AFP cases were missed from active surveillance. As an additional quality assurance measure, periodic audits were undertaken by investigators of case medical records to assess accuracy of data collected for some conditions.

Data management

PAEDS utilises web-based secure data management systems, enabling online data entry by surveillance nurses at each site and centralised data extraction. Data are held securely and exported on a regular basis by staff at the PAEDS coordinating centre for clinical review, monthly quality checks, analysis and reporting. Previously, the majority of PAEDS conditions have been

managed in the WebSpirit database system,⁹ with some conditions held in REDCap.^{10,11} In 2019, a transition plan to migrate all conditions to REDCap was developed. In addition to data from the two conditions (FluCAN and IGAS)

already held in REDCap, data for four other conditions under surveillance — AFP, ACE, KD and GNBSI — were transitioned into REDCap by the end of 2019.

Table 1: PAEDS conditions under surveillance, case definitions and rationale, 2019

Condition and case definition	Rationale
<p>Acute flaccid paralysis (AFP) <i>Case definition:</i> Any child aged from birth to < 15 years and presenting with acute flaccid paralysis: onset of flaccid paralysis in one or more limbs or acute onset of bulbar paralysis.</p>	<p>WHO requires active national surveillance for cases of AFP in children aged < 15 years in order to monitor for potential cases of paralytic poliomyelitis. PAEDS collaborates with the APSU in nationwide surveillance in an effort to meet the target enrolment of 1 non-polio case per 100,000 children aged < 15 years. Data collected on AFP also contribute to separate analysis for SANE.^a</p>
<p>Acute childhood encephalitis (ACE) <i>Case definition:</i> Any child aged from birth to < 15 years AND hospitalised with acute encephalopathy AND who has <i>one or more</i> of the following: fever, seizures, focal neurological findings, at least one abnormality of cerebrospinal fluid, or EEG/neuroimaging findings consistent with infection-related encephalitis.</p>	<p>Encephalitis is a critical condition that is considered a marker syndrome for emerging infectious diseases. It is most often caused by viruses (including those which are or potentially will be vaccine preventable). It can also be immune-mediated, and uncommonly can be associated with vaccine receipt. As there are limited epidemiologic data on encephalitis, PAEDS is uniquely placed to undertake active, syndromic surveillance, and can collect biological specimens. Enrolment of participants into comprehensive follow-up studies to improve understanding of long-term neuropsychological sequelae also occurs.¹² Data collected on ACE also contribute to separate analysis for SANE.^a</p>
<p>Influenza – FluCAN (Seasonally: April–October) <i>Case definition:</i> Any child aged from birth to < 18 years who is hospitalised, clinically suspected of having influenza (respiratory symptoms +/- fever) and confirmed influenza PCR-positive.</p>	<p>The emergence of H1N1-09 influenza in 2009 demonstrated the importance of enhanced influenza surveillance in children.¹³ PAEDS provides unique timely sentinel data from 6 states/territory around Australia (Sydney, Perth, Brisbane, Melbourne, Adelaide and Darwin) on influenza hospitalisations, including complications and deaths, which can be used to inform public health response and policy. The data on children supplement adult data from 15 other FluCAN sites. Information on influenza test-negative (control) patients with acute respiratory illness (ARI) is also collected and allows calculation of vaccine effectiveness to be performed.</p>
<p>Social research (Seasonally: April–October) Parents of any child aged from birth to < 18 years who is hospitalised, clinically suspected of having influenza (respiratory symptoms +/- fever) and confirmed influenza PCR-positive or PCR-negative</p>	<p>Influenza vaccine uptake in Australia is low. In 2018, when most Australian jurisdictions funded influenza vaccination for all children aged between six months and five years, uptake was estimated to be 25.6%.¹⁴ Though this was a fivefold increase in uptake compared to 2017, three-quarters of eligible children remained unvaccinated. Most children hospitalised with laboratory-confirmed influenza represent the vaccine-preventable disease burden and thus give insight into how policy and/or practice can be improved and prioritised in order to increase influenza vaccine uptake. Therefore, the primary aim of this body of research was to understand attitudes about and access to influenza vaccination experienced by parents of children hospitalised for ARI.</p>
<p>Intussusception (IS) <i>Case definition:</i> Any child aged < 9 months presenting with a diagnosis of acute intussusception confirmed using the Brighton Collaboration clinical case definition (Level 1 or 2). Includes hospitalised or ED only.¹⁵</p>	<p>Intussusception is the most common cause of bowel obstruction in infants and young children and was associated with a previous rotavirus vaccine in the USA which was withdrawn in 1999. Timely, active and systematic surveillance of IS cases is important and has identified a temporal but low incidence association with the rotavirus vaccines currently available under the NIP (since July 2007).¹⁶ Surveillance also aims to describe the epidemiology, aetiology and severity of IS.^{17,18}</p>
<p>Pertussis <i>Case definition:</i> <u>Hospitalised pertussis</u> - Any child aged from birth to < 15 years hospitalised with laboratory confirmed pertussis. <u>Pertussis vaccine effectiveness study</u> - Any child aged from birth to < 6 months with laboratory-confirmed pertussis identified from either the 'Hospitalised pertussis' study (above) or from the ED.</p>	<p>Despite immunisation coverage approaching 93%, pertussis continues to cause significant morbidity and mortality, particularly in very young Australian children.¹⁹ The aims of this surveillance are to determine the burden of disease from hospitalised pertussis, with special emphasis on the duration of hospitalisation, use of intensive care, death and disability. Possible sources of infection and co-morbidities to severity of pertussis are examined. The adjunct study seeks to estimate the effectiveness of pertussis vaccination (either in infancy or maternal) against pertussis hospitalisations and emergency department presentations by comparing pertussis vaccination status in infants with pertussis < 6 months of age and test-negative controls. These surveillance data will assist in optimising pertussis prevention strategies.</p>

a SANE: Serious acute neurological event.

Condition and case definition	Rationale
<p>Varicella zoster virus (VZV) infection <i>Case definition:</i> Any child aged from birth to < 15 years hospitalised for varicella or herpes zoster with or without complications.</p>	<p>Complications of varicella or herpes zoster requiring hospitalisation provide a measure of disease burden and severity. Ongoing surveillance aims to show trends in incidence and severity of both varicella and herpes zoster related to the varicella vaccination program and allow vaccine effectiveness estimations.²⁰ The timely collection of vesicle samples and genetic subtyping of varicella-zoster virus infection allows for identification of vaccine failures in immunised children and genotypes associated with severe complications or derived from the live attenuated vaccine.</p>
<p>Invasive meningococcal disease (IMD) Any child aged from birth to < 18 years who is hospitalised with laboratory confirmed invasive meningococcal disease.</p>	<p>IMD causes death in young healthy children and adolescents in 5–10% of cases.^{21–23} No other infectious disease has such debilitating consequences following resolution of the infection, with 20–57% of surviving children developing long term complications including amputation, cerebral infarction and severe skin scarring.^{24–26} Surveillance of IMD will enable identification of serogroup/genotypes causing disease and any associations between serogroup and severity of disease and sequelae and presenting clinical features. This study also seeks to estimate vaccine effectiveness against meningococcal disease and disease severity in IMD cases pre and post introduction of meningococcal vaccine programs in Australia.</p>
<p>Invasive group A streptococcus (IGAS) Any child aged from birth to < 18 years hospitalised with laboratory confirmed invasive group A streptococcus disease.</p>	<p>The group A beta-haemolytic streptococcus is a common infective agent in children and adults that causes the widest range of clinical disease in humans of any bacterium. Invasive disease (IGAS identified in a sterile site) is less common, but has high rates of mortality and long-term morbidity. Group A streptococcal toxin mediated diseases include streptococcal toxic shock syndrome (STSS), which is usually found in association with invasive disease and has a case fatality rate over 50%.^{27,28} There is no vaccine currently available for prevention of streptococcal infection although research is underway. Further epidemiological data on incidence, severity, clinical features and pathogen characteristics (genotype) are warranted.</p>
<p>Kawasaki disease (KD) Any child aged from birth to < 16 years hospitalised with Kawasaki disease.</p>	<p>KD is a childhood vasculitis of unknown aetiology. It is the commonest cause of acquired heart disease in children in the developed world.²⁹ KD has a number of significant sequelae including coronary artery aneurysms, myocarditis, myocardial infarction and arrhythmia.²⁹ Adult survivors of KD continue to be at risk of cardiac complications with higher rates of myocardial infarction and premature death extending the disease burden beyond childhood.³⁰ The incidence of KD internationally is increasing markedly³¹ and it is thought to have an incidence of 3–15 children < 5 years old per 100,000 per year in Australia.³² Ascertaining the exact burden of the disease in Australia has been difficult as there is no national disease registry as exists elsewhere in the world. Understanding the childhood disease patterns and therapeutic response will allow development of effective treatment to reduce short- and long-term sequelae and allow investigation of the possible aetiology of KD. A better understanding of intravenous immunoglobulin (IVIg) prescription patterns and the use of adjunctive therapies will allow the development of national therapeutic guidelines, improved patient outcomes and opportunities for future research into more effective treatment regimens.</p>
<p>Gram-negative bloodstream infections (GNBSI) Any child aged from birth to < 18 years hospitalised with laboratory confirmed gram-negative bloodstream infection.</p>	<p>Bloodstream infections (BSI) in children are increasingly healthcare-associated and occur in those with complex comorbidities. Gram-negative organisms cause almost one half of all BSI in children and are associated with significant mortality.³³ In an era of increasing antimicrobial resistance, GNBSI represent a significant concern.³⁴ The development and evaluation of new, effective antimicrobials for resistant gram-negative infections is particularly limited in children.³⁵ Existing surveillance systems rarely capture paediatric-specific data. This surveillance is necessary to understand the clinical and molecular epidemiology of GNBSI and multi-drug resistant GNBSI in children. It will augment data collected by the Australian Group on Antimicrobial Resistance (AGAR) Gram-Negative Sepsis Outcome Program (GNSOP) and will help to inform risk factors for an optimal treatment of antimicrobial-resistant gram-negative infections in children.</p>

Table 2: Site participation in PAEDS conditions under surveillance, 2019

	CHW-NSW	RCH- VIC	MH-VIC	QCH-QLD	WCH-SA	PCH-WA	RDH-NT	SCH-NSW
Acute flaccid paralysis	✓	✓	✓	✓	✓	✓	✓	X
Intussusception	✓ ^a	X						
Varicella zoster virus	✓	✓ ^a	✓ ^a	✓	✓ ^a	✓ ^a	✓ ^a	X
Hospitalised pertussis	✓ ^a	✓	✓	✓	✓ ^a	✓ ^a	✓	X
Pertussis vaccine effectiveness	✓	✓	X	✓	✓	✓	✓	X
Acute childhood encephalitis	✓	✓	✓ ^b	✓	✓	✓	✓ ^b	X
Influenza (FluCAN)	✓	✓	✓	✓	✓	✓	✓	X
Invasive meningococcal disease	✓ ^a	✓ ^a	✓ ^a	✓ ^a	✓	✓	✓ ^a	X
Invasive group A streptococcus disease	X	✓	✓	✓	X	✓	✓	X
Kawasaki disease	✓	✓	✓	✓	✓	✓	✓	X
Gram-negative bloodstream infection	✓	✓	X	✓	X	✓	X	✓
Social research	✓	X	✓	✓	✓	✓	✓	X

a 1 January – 30 June 2019.

b 1 July – 31 December 2019.

Table 3: Total hospital admissions and ED presentations (including admitted patients) for the seven hospitals participating in PAEDS in 2019

2019			
PAEDS site ^a	Hospital admissions	ED presentations	Total PAEDS cases, all conditions (% hospital admissions) ^b
CHW, Sydney	35,855	64,098	692 (1.9)
RCH, Melbourne	52,202	91,991	634 (1.2)
WCH, Adelaide	21,114	47,431	236 (1.1)
PCH, Perth	30,701	69,674	303 (1.0)
QCH, Brisbane	40,512	73,460	403 (1.0)
RDH, Darwin	9,432	12,700	48 (0.5)
MH, Melbourne	13,140	70,633	385 (2.9)
Total	202,956	429,987	2,701 (1.3)

a See Table 2 for sites participating in conditions under surveillance.

b Denominator used is hospitalisations. Some cases, e.g. intussusception, pertussis (< 6 months of age for VE study), may not be included as they may be treated in ED only.

Results

In 2019, there were 202,956 admissions at the seven participating PAEDS sites (Table 2). PAEDS identified 2,701 cases of the ten conditions under surveillance across all PAEDS sites in 2019 (Table 3). Data on an additional 1,450 influenza test-negative controls were collected under FluCAN surveillance and a further 48 pertussis test-negative controls were collected for a vaccine effectiveness study.

Since the inception of PAEDS in 2007, a total of 10,766 cases (excluding controls) have been recruited.

Condition-specific surveillance results for 2019 and recent baseline case detection

Table 4 shows case numbers for all ten conditions per year.

Acute flaccid paralysis

PAEDS reported 55 cases of AFP to the NERL in 2019, meeting the national surveillance target of 1 non-polio AFP case per 100,000 children aged < 15 years⁷ (the estimated Australian population in this age group was 4.74 million in 2019, yielding 1.2 cases per 100,000 children aged <15 years).³⁶ Of these 55 cases, at least one stool sample was collected within two weeks of onset of paralysis for 42 cases (76%), and two stool samples were collected for 29 cases (53%). The most common diagnoses associated with AFP were Guillain-Barré syndrome (GBS; 27%), transverse myelitis (24%) and acute demyelinating encephalomyelitis (ADEM; 7%). The Australian Government Department of Health Polio Expert Panel (PEP) sub-classified three cases as acute flaccid myelitis (AFM), one of whom showed detection of enterovirus A71 in stool, an important regional cause of severe neurological illness in children.

Table 4: Number of cases captured by PAEDS in 2019 by condition, including comparison to 2018

Condition	Total cases captured by active surveillance 2019	Total cases captured by active surveillance 2018
Acute flaccid paralysis	55	50
Intussusception	29 ^a	53
Varicella or herpes zoster	25 ^b	47
Pertussis	40 ^b	44
Acute childhood encephalitis	157	143 ^c
Influenza ^d	1,850	426
Invasive meningococcal disease	22 ^b	53
Invasive group A streptococcus	48 ^b	109
Kawasaki disease	190	N/A ^e
Gram-negative bloodstream infections	285 ^f	N/A
Total	2,701	N/A

a All sites ceased surveillance in July 2019.

b Limited site participation in surveillance condition (Table 2).

c Excluding RDH and MH.

d An additional 1,450 influenza test-negative controls were captured for 2019 by the PAEDS network.

e N/A: not applicable.

f Excluding SCH, Randwick cases (n = 12).

Vaccine-proximate cases were clinically reviewed and any that were deemed plausibly consistent with an AEFI were reported via existing channels. In 2019, two cases were reported, both with documented receipt of influenza vaccine, one of these with receipt of other vaccine types as well.

Acute childhood encephalitis

PAEDS identified 157 cases of suspected ACE in 2019. The highest number of cases (20/157; 13%) was recorded in August, consistent with previous winter peaks observed in prior years. All ACE cases underwent a review process by an expert panel and were classified as: infectious 63/157 (40%); immune-mediated 27/157 (17%); unknown 15/157 (10%); and 'not encephalitis' 52/157 (33%). Influenza virus was detected in 16/105 encephalitis cases tested (15%), with the highest frequency observed in August; influenza was detected in four cases presenting prior to the influenza season. Herpes simplex virus and enteroviruses were detected in 9/105 (9%) cases each; parechovirus was detected in 3/105 (3%) cases. The most frequent bacterial pathogens detected were *Mycoplasma pneumoniae*, 8/105 (8%), and *Streptococcus pneumoniae*, 5/105 (5%). Just over half of the suspected ACE cases (82/157; 52%) were admitted to intensive care, and 12/105 (11%) of the cases classified as confirmed encephalitis died. Influenza was detected in five of these deaths, with four of these aged < 5 years; herpes simplex virus was detected in three cases; enteroviruses were detected in two cases; and the final two cases had a mix of pathogens detected.

Following clinical review, five suspected ACE cases were assessed as AEFI and were reported via existing channels. Of these, two cases had documented receipt of influenza vaccine, and both had also received other vaccine types.

Influenza

During the 2019 influenza season (April–October), 1,850 children were hospitalised with laboratory-confirmed influenza across the

PAEDS network: CHW (470); RCH (402); MH (313); WCH (201); PCH (200); QCH (227); and RDH (37). Of these children, 203 (11%) were aged < 6 months, 835 (45%) were aged between 6 months and < 5 years and 812 (44%) were aged ≥5 years. Influenza A was detected among 1,209 cases (65%) and Influenza B among 618 cases (33%); 23 cases (1%) had multiple sub-types detected. In addition, 1,450 influenza test-negative controls were enrolled, to support calculation of vaccine effectiveness. Of the hospitalised influenza cases, 800/1841 (43%) had underlying medical conditions, 167/1850 (9%) were admitted to intensive care units and 11/1839 (0.6%) died. Influenza vaccine uptake among cases was reported for 212/810 (26%) children aged between 6 months and < 5 years and 812 (44%) were aged ≥5 years. Among infant cases aged < 6 months, maternal vaccination status was ascertained in 166 paired mothers, with 60 (36%) reporting vaccination for influenza during pregnancy. Among controls, vaccine uptake was reported for 341/758 (45%) children aged between 6 months and < 5 years and 812 (44%) were aged ≥5 years. Among infant controls aged < 6 months, maternal vaccination status was ascertained in 292 mothers. Of these, 122 (42%) were vaccinated during pregnancy.

Social research

In 2019, 595 parents/guardians of children hospitalised in five PAEDS/FluCAN sites for acute respiratory illness (± laboratory-confirmed influenza) participated in an online survey. The survey was informed through our qualitative interviews with parents of children hospitalised for influenza³⁷ and sought to measure parents/guardians' capability, opportunity and motivation to vaccinate.³⁸ Of the 595 parents/guardians who participated, 58% (342) of their hospitalised children (342/595) were aged 6–59 months, 47% (282) had ≥ 1 comorbidities, 68% (406) were influenza-positive, and 71% (421) were not vaccinated prior to hospitalisation. We identified that the strongest barriers to influenza vaccination of children prior to hospitalisation were:³⁹ lack of health care provider recommendation; difficulties in remembering to make an

appointment to vaccinate; difficulties in getting an appointment for vaccination; perceiving that other parents were also not vaccinating their children against influenza; general lack of support of influenza vaccination of children; and a lack of history of influenza vaccination of the child and parent.

Intussusception

In 2019, there were 29 cases of IS identified, of which 21 (72%) met Brighton level 1 criteria. Five cases (24%) had received a rotavirus vaccine in the 21 days preceding intussusception: one case occurred following the first dose, and four cases occurred following the second dose of the vaccine. Of the 21 cases of level 1 IS, four children (19%) required surgery and 17 (81%) were resolved with air/hydrostatic enema. Of the five children who had IS within 21 days of vaccination, two (40%) required surgery (ages 8 and 20 weeks) and three (60%) were successfully treated with air/hydrostatic enema. There were no deaths.

Pertussis

In 2019, there were 40 eligible children with laboratory-confirmed pertussis identified across the PAEDS network. The median age was 4 months, with a range of 1 week to 14 years. Of identified cases, 37/40 were children eligible for vaccination (aged 6 weeks or greater; 27 were aged 6 weeks to < 12 months, and ten were aged \geq 12 months to 14 years). Of these children, 31/37 (84%) had received a dose of pertussis-containing vaccine prior to presenting to hospital with pertussis (22 children aged 6 weeks to < 12 months, and nine children aged \geq 12 months to 14 years). Of the 3/40 cases who were infants aged < 6 weeks, the mothers of two had not received a pertussis-containing vaccine during pregnancy, while the mother of one child had received a pertussis-containing vaccine at a gestational age of 23 weeks. No children required admission to an intensive care unit.

Varicella and herpes zoster

In 2019, there were 25 cases of varicella-zoster virus infection identified across the PAEDS network (20 varicella; five herpes zoster). Of these 25 children, 15 (60%) were eligible for NIP-funded varicella vaccination; where vaccination status was ascertained, 11/14 (79%) had been vaccinated. Amongst these cases, a minority reported complications. These included: ataxia (1/23; 4%); hepatitis (1/23; 4%); dehydration (4/21; 19%); and secondary bacterial infection (2/23; 9%).

Invasive meningococcal disease

In 2019, there were 22 cases of IMD identified across the PAEDS network. Of these cases, 15/22 (68%) were aged < 5 years, and 6/22 (27%) were < 12 months of age. Five cases (23%) were aged between 5 and 15 years, and two were aged \geq 15 years. Serogroup B was the predominating strain (16/22 cases); 12/16 of these (75%) were in children aged < 5 years. One of these children (aged 2 years) had received an incomplete course of meningococcal B vaccine (one dose when aged < 23 months); the remainder were unvaccinated for meningococcal B. Serogroup W was identified in three cases and serogroup Y in one case: none of these children were vaccinated for serogroups A, C, W-135 and Y with quadrivalent vaccine. Serogroup C was identified in one case, and this child had not been vaccinated for meningococcal C. The serogroup could not be determined for one case. Nine cases (9/22; 41%) had meningitis and 18/22 (82%) were septicaemic; six of these children had both meningitis and septicaemia. The most common reported symptoms on presentation were fever (21/22; 96%); rash (18/22; 82%); lethargy (17/21; 81%); unwell appearance (16/22; 73%); vomiting (16/22; 73%); irritability (14/21; 67%); and refusal to eat or drink (14/22; 64%). Eleven children (50%) were admitted to the intensive care unit (ICU), and one death occurred.

Invasive group A streptococcus

In 2019, IGAS surveillance was reduced to five sites: RCH, MH, QCH, PCH and RDH. There were 48 IGAS cases admitted to participating PAEDS sites. In addition to hospital data, PAEDS surveillance teams contacted these cases six months after discharge to assess longer-term outcomes.

Kawasaki disease

In 2019, there were 190 cases of KD admitted across the PAEDS network. The median age was 3 years and the male to female ratio was 1.7:1. Of the children admitted, 99% (188/190) received at least one dose of IVIG, whilst 22% (42/190) received two or more doses of IVIG. Admission to the intensive care unit was required for 4% of children (7/183).

Gram-negative bloodstream infections

In this first year of surveillance, 297 clinical episodes of GNBSI were identified (285 at PAEDS sites and 12 at SCH; see Table 4). Among the 297 episodes, the median age was 39 months (interquartile range (IQR) 7 to 90 months). Sixty-two percent of episodes occurred in males, and 7% in children from families identifying as Aboriginal or Torres Strait Islander. While a majority of infections (56%) had community onset, almost 70% occurred in children with significant comorbidities, and 57% occurred in children with indwelling central venous catheters. The most frequent comorbidities identified were malignancies. More than 40% of episodes had no focus of infection, and the most commonly-recorded foci were central venous catheter-associated BSI (51) and urinary tract infection (44). The predominant organisms identified were *Escherichia coli* (83); *Salmonella* species (44); *Klebsiella* species (36); *Enterobacter* species (28); and *Pseudomonas* species (28). Sixteen infections were polymicrobial. All BSI caused by *Salmonella* had community onset, and cases with *E. coli* were also more likely to present from the community. Cases with other Enterobacterales and with non-fermenting

bacteria were more likely to have hospital onset. The most frequent sequence type (ST) observed in *E. coli* was ST95. No dominant sequence types were identified in other species by whole genome sequencing. One quarter of *E. coli* and *Klebsiella pneumoniae* (27/106) were resistant to third generation cephalosporins. A single carbapenem-resistant *Enterobacter cloacae* was identified, not associated with detection of a carbapenamase gene. IMP-4 was detected in two other isolates, both these were phenotypically susceptible to meropenem. One third of *Pseudomonas aeruginosa* (8/25) were MDR, though only two were carbapenem-resistant. Resistance in *P. aeruginosa* was observed to ceftolozane-tazobactam (3/24) and ceftazidime-avibactam (5/25). Death occurred in 8% of all episodes (25/297). Thirty-six children were inpatients in ICU at the time of BSI onset; a further 29 required ICU admission. The median duration of hospital stay was 12 days (IQR 6 to 32 days); 63 children were discharged to an outpatient antimicrobial administration service.

Discussion

Since 2007, PAEDS has collected and reported novel and unique data on hospitalisation due to uncommon serious childhood conditions. In 2019, PAEDS expanded its surveillance through partnerships with grant funded research whilst maintaining its performance with respect to its core public health surveillance function. PAEDS has continued its role of reporting enhanced clinical and vaccination data to public health partners, describing detailed clinical epidemiological features of severe childhood conditions.

PAEDS surveillance of AFP continues to report the majority of cases into national AFP surveillance, enabling Australia to meet the WHO AFP case detection target for poliomyelitis surveillance for 2019.⁷ Ongoing difficulty achieving adequate stool collection rates from AFP cases continues to be a challenge. PAEDS nurses facilitated collection of two stool samples in 53% of PAEDS AFP cases ascertained in 2019 and continue to aim to meet the WHO surveillance target of adequate stool collection in 80% of cases.^{7,40} To improve

performance, PAEDS implemented a nurse-led action plan in July 2019, with standardised data collection to identify the barriers that contribute to unsuccessful stool specimen collection. Early data from 2020 indicate that the stool collection rate is improving. The newly-recognised and emerging syndrome, AFM, associated with non-polio enteroviruses—initially identified in the United States of America and Europe in 2014—has since been recognised in Australia, with a cluster noted retrospectively in March 2016 in a review of PAEDS data.⁴¹ The PEP has since begun sub-categorising AFP cases as AFM guided by US Centers for Disease Control and Prevention (CDC) definitions to enhance monitoring of this syndrome in Australia; three PAEDS AFP cases were sub-categorised as AFM in 2019, one associated with the important neuro-tropic non-polio enterovirus, EVA71.

PAEDS encephalitis surveillance continues to support early detection of epidemic infectious diseases in children. ACE is a severe syndrome with half of the cases identified requiring admission to intensive care, and with high case fatality. Encephalitis-associated pathogens observed in 2019 were consistent with those previously described as leading infectious causes of childhood encephalitis.^{12,42} Notably, influenza was the leading cause of ACE-related death in 2019. PAEDS data on ACE have previously highlighted the burden of influenza-associated neurological disease, particularly in otherwise-well children aged < 5 years, supporting the funding of vaccine programs aimed at influenza prevention in this age group.⁴³ These severe, albeit rare, manifestations of paediatric influenza are monitored by PAEDS, which will contribute to program evaluation over time. PAEDS surveillance of ACE also enables identification of cases with influenza detected outside the usual influenza season (November–March), with 4/16 (25%) out-of-season influenza-associated ACE cases in 2019. Severe ACE cases (those deceased or requiring intensive care admission) were notified by PAEDS to the Australian Government Department of Health and the respective recruiting site's state health departments in near real-time. In 2019, with the Australian Government Department

of Health provision of funding support for ACE surveillance, PAEDS-ACE investigators have successfully improved the efficiency of data collection and subsequent case review and reporting.

In 2019, the influenza season saw high activity which commenced and peaked approximately five weeks earlier than the average for the previous five years,⁴⁴ nonetheless, despite large case numbers, clinical severity overall remained low.⁴⁵ For children aged 6 months to < 5 years, seasonal vaccination was funded by all states and territories across Australia in 2019 and vaccine uptake was 45%, an improvement of nearly 10% compared to 2018.^{4,46} Vaccine uptake was lower (40%) for children > 5 years, as was maternal vaccine uptake among test-negative control infants aged < 6 months at 42%; however, due to infant age and availability of vaccination during pregnancy, not all mothers would have been able to access vaccination. Continued effort is needed to promote the importance of vaccination among all ages,³⁹ especially for at-risk groups, with 2019 a reminder of the unpredictability and burden of seasonal influenza. Point estimates of vaccine effectiveness ranged from 43% to 70% for 2019 using data from the entire FluCAN network, consisting of adults and children > 6 months, with the greatest protection seen against influenza A (H1N1).⁴⁴ Continued surveillance and timely reporting of paediatric influenza hospitalisation data is important to inform policy and practice on immunisation programs impacting all Australian children.

Data collected by PAEDS have been instrumental in quantifying the association between IS and rotavirus vaccine when given to infants.^{15–17} Given the documented but low vaccine-associated risk, IS surveillance has been suspended by PAEDS, but could be reactivated in the setting of any vaccine or program changes.

Despite vaccination, pertussis remains endemic in Australia with epidemics occurring every 3–4 years.^{19,47} Infants too young for vaccination, or those for whom vaccination is delayed, are at the highest risk of severe morbidity and mortality.^{19,47} In 2019, ninety-two percent of the 37 cases were

eligible for vaccination; most eligible cases (82%) had received at least one dose of pertussis-containing vaccine. Since 2015, early infant protection via maternal vaccination during each pregnancy has been recommended, and antenatal pertussis vaccination has been funded since 2018;⁴⁸⁻⁵⁰ however, in 2019, only one of three mothers of infant cases aged < 6 weeks had received a pertussis-containing vaccine during pregnancy. Continued surveillance can provide additional evidence to inform expectant parents, immunisation providers and policy makers of the importance of timely pertussis vaccination.

There were fewer varicella-related hospitalisations in 2019 than in 2017 or 2018,⁴ acknowledging the reduction in participating PAEDS sites with only two sites (CHW and QCH) continuing surveillance from July 2019. As the varicella vaccine program has now been in place for 15 years on the National Immunisation Program, there is considerable evidence of a reduction nationally in varicella cases, notwithstanding Australia maintaining a one-dose schedule with expected lower efficacy than a two-dose program.⁵¹ Changing the vaccine schedule from a monovalent varicella vaccine to a combined measles, mumps, rubella varicella vaccine has not shown any reduction in vaccine effectiveness.

There were fewer cases of IMD in 2019 than in 2018,⁴ acknowledging the reduction in participating PAEDS sites with only two sites (WCH and PCH) continuing surveillance from July 2019. At both of these sites fewer cases were identified in 2019 than in 2018 (WCH 8 and 14 cases; PCH 4 and 8 cases in 2019 and 2018 respectively). Serogroup B was the dominant strain in hospitalised children nationally. This is expected, as serogroup W disease, which predominated during the serogroup W outbreak in 2016–2018, has now reduced following the introduction of national meningococcal ACWY vaccine programs in 2018 (at 12 months) and 2019 (adolescents and young adults aged 15–19 years), which followed earlier state funded programs and may also explain the reduction in

IMD cases in 2019. As meningococcal B vaccine has been included on the National Immunisation Program from 1 July 2020 for Aboriginal and Torres Strait Islander infants up to 2 years of age and people of any age with specific risk conditions, and in a state-funded program for infants and adolescents in South Australia, monitoring of vaccine effectiveness and impact remains important. Any IMD cases in vaccinated children will be investigated through PAEDS.

PAEDS continues to monitor IGAS admissions in comparison to the low number of viral infections, including seasonal influenza, which have been associated with seasonal increases in cases in the past. Future projects include determining the cost burden of IGAS at paediatric hospitals via the PAEDS sites. This will be important health economics data as Group A streptococcal vaccines come down the pipeline.⁵²

Kawasaki disease is a leading cause of acquired heart disease in children with the potential to cause lifelong damage to the coronary arteries. While there is an effective treatment (IVIG), the diagnosis of KD remains challenging, as there is no diagnostic test that can reliably differentiate KD from other conditions. Surveillance undertaken by the PAEDS network is providing important insights into the diagnostic and treatment decisions that clinicians make regarding KD. In contrast to other published studies,⁵³ our data show that Australian clinicians have a generally unified approach to the treatment of KD. We intend to further analyse these data to better understand how clinicians approach the care of more complicated cases, and to estimate the burden of coronary disease in children that is attributable to KD.

The treatment of invasive gram-negative infections in children is increasingly complicated by antimicrobial resistance. Paediatricians need access to new antimicrobial agents, informed by evidence generated in studies that include children. Surveillance undertaken by the PAEDS network is providing systematic data that will inform the clinical management of these complicated infections in hospitalised children. As

reported elsewhere, our data reveal a significant burden of healthcare-associated and hospital-acquired infections. Morbidity (including prolonged hospital and ICU stay) and mortality are substantial. Already, notable differences can be observed between our data and those captured by existing surveillance systems that focus on adult patients and on antimicrobial-resistant infections alone. Our comprehensive surveillance will allow us to draw important inferences regarding risk factors for antimicrobial resistance, and adverse outcomes. Furthermore, whole genome sequencing will allow us to explore transmission dynamics in both susceptible and resistant infections. Surveillance continues in 2020 and results to date have supported leveraging of further funding through a successful NHMRC Investigator award.

The PAEDS system is limited by the now-variable participation in surveillance for some conditions (VZV, pertussis, IMD, IGAS) across the network. This impacts on the network's capacity to obtain a nationally representative picture for these conditions of interest. However, by having some sites continuing surveillance and retaining the data collection capability, the network has the ability to rapidly re-activate surveillance for these conditions in any jurisdiction or nationally in response to a public health need. Further, as a sentinel surveillance system, PAEDS cannot directly calculate age-specific population incidence rates of the conditions under surveillance, although ongoing efforts are directed to optimally determining the population coverage of our network's hospitals. Additionally, PAEDS demographic and geographic coverage, whilst enhanced by the inclusion of MH and RDH, could be further enriched in the future.

PAEDS continues to be an important capacity-building initiative to enhance existing public health surveillance for serious childhood conditions, particularly VPDs and AEFIs, with the overarching aim of improving child health outcomes. PAEDS has demonstrated its agility as a network by responding to jurisdictional public health needs in 2019. The PAEDS network is a unique surveillance platform that

has the potential to be used for other urgent or research-focused studies for which active surveillance is optimal. In 2020, this capability has been used to support the national response to the COVID-19 pandemic through active surveillance of hospitalised COVID-19 in children, including complications.⁵⁴ The PAEDS network continues to actively consider future child health priorities in Australia, and actively engage with similar networks internationally⁶ to further optimise surveillance.ⁱ

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ⁱ More information on PAEDS is available at <https://www.paeds.edu.au>.

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Appendix A

Table A.1: Table of acronyms

Acronym	Description
ACE	Acute childhood encephalitis
AIR	Australian Immunisation Register
ADEM	Acute demyelinating encephalomyelitis
AEFI	Adverse events following immunisation
AFM	Acute flaccid myelitis
AFP	Acute flaccid paralysis
APSU	Australian Paediatric Surveillance Unit
ARI	Acute respiratory illness
BSI	Bloodstream infection
CDC	Centers for Disease Control and Prevention
CHW	The Children's Hospital at Westmead
ED	Emergency department
FluCAN	Influenza Complications Alert Network
FS	Febrile seizures
GBS	Guillain Barré syndrome
GNBSI	Gram-negative bloodstream infections
ICD	International Classification of Diseases
IMD	Invasive meningococcal disease
IGAS	Invasive group A streptococcus
IS	Intussusception
IVIG	Intravenous immunoglobulin
LCCH	Lady Cilento Children's Hospital Brisbane
MH	Monash Health Victoria
NCIRS	National Centre for Immunisation Research and Surveillance
NERL	National Enterovirus Reference Laboratory
NESB	Non-English speaking background
NHMRC	National Health and Medical Research Council
NIP	National Immunisation Program
NSW	New South Wales
PAEDS	Paediatric Active Enhanced Disease Surveillance
PCH	Perth Children's Hospital
QCH	Queensland Children's Hospital
RCH	The Royal Children's Hospital Melbourne
RDH	Royal Darwin Hospital, Northern Territory
SANE	Serious acute neurological event
VE	Vaccine effectiveness
VIDRL	Victorian Infectious Diseases Reference Laboratory
VPD	Vaccine preventable diseases
VZV	Varicella zoster virus
WCH	The Women's and Children's Hospital Adelaide
WHO	World Health Organization