Annual report

Paediatric Active Enhanced Disease Surveillance (PAEDS) annual report 2015: Prospective hospital-based surveillance for serious paediatric conditions

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Abstract

Keywords: paediatric, surveillance, child, hospital, vaccine preventable diseases, adverse event following immunisation, acute flaccid paralysis, encephalitis, influenza, intussusception, pertussis, varicella zoster virus

Abstract

Introduction: The Paediatric Active Enhanced Disease Surveillance (PAEDS) network is a 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). PAEDS data is used to better understand these conditions, inform policy and practice under the National Immunisation Program, and enable rapid public health responses for certain conditions of public health importance. PAEDS enhances data available from other Australian surveillance systems by providing prospective, detailed clinical and laboratory information on children with selected conditions. This is the second of the planned annual PAEDS reporting series, and presents surveillance data for 2015.

Methods: Specialist surveillance nurses screened hospital admissions, emergency department records, laboratory and other data, on a daily basis in 5 paediatric tertiary referral hospitals in New South Wales, Victoria, South Australia, Western Australia and Queensland to identify children with the selected conditions. Standardised protocols and case definitions were used across all sites. Conditions under surveillance in 2015 included acute flaccid paralysis (a syndrome associated with poliovirus infection), acute childhood encephalitis (ACE), influenza, intussusception (IS; a potential AEFI with rotavirus vaccines), pertussis and varicella-zoster virus infection (varicella and herpes zoster). Most protocols restrict eligibility to hospitalisations, ED only presentations are also included for some conditions.

Results: In 2015, there were 674 cases identified across all conditions under surveillance. Key outcomes of PAEDS included: contribution to national AFP surveillance to reach WHO reporting targets; identification of signals for *Mycoplasma pneumoniae* and parechovirus-related outbreaks (ACE surveillance); and demonstration of high influenza activity with vaccine effectiveness (VE) analysis supportive of vaccination. Surveillance for IS remains ongoing with any identified AEFIs reported to the relevant State Health Department; varicella and herpes zoster case numbers decreased slightly from previous years in older children not eligible for catch-up. Pertussis case numbers increased in early 2015 and analysis of cases in children aged <1 year demonstrated the importance of timely childhood and maternal immunisation.

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

Introduction

This is the second annual report of the Paediatric Active Enhanced Disease Surveillance (PAEDS) network and summarises data collected in 2015. PAEDS historical data for 2007–2014, including impacts and outcomes, were reported in the PAEDS 2014 inaugural report.[1]

PAEDS is a hospital-based active surveillance system for serious childhood conditions of public health importance, particularly vaccine preventable diseases (VPDs) and adverse events following immunisation (AEFI). PAEDS, through prospective case identification and ascertainment, collects timely and detailed clinical data on children requiring hospitalisation for select conditions. In some instances, emergency department (ED) presentations are also included. PAEDS data is used to better understand these conditions, inform policy and practice under the National Immunisation Program (NIP) and enable rapid public health

responses for certain conditions of public health interest. PAEDS is well positioned compared to other passive surveillance programs that are usually less able to adequately capture such timely and comprehensive data.[2]

During 2015, the PAEDS network consisted of 5 participating hospitals: The Children's Hospital at Westmead (CHW), Sydney, New South Wales (NSW); Royal Children's Hospital (RCH), Melbourne, Victoria; Women's and Children's Hospital (WCH), Adelaide, South Australia; Princess Margaret Hospital (PMH), Perth, Western Australia; and Lady Cilento Children's Hospital (LCCH), Brisbane, Queensland. PAEDS is coordinated by the National Centre for Immunisation Research and Surveillance (NCIRS) based at CHW in Sydney.

PAEDS activities are supported through funding by the Australian Government Department of Health and the 5 participating states' health departments. 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.

Methods

Active case ascertainment

Under PAEDS, specialist surveillance nurses in each hospital identified children diagnosed with the conditions under surveillance, as defined in Table 1, by reviewing admission and emergency department databases, clinical records, laboratory logs and through liaison with medical and nursing staff.[1]

For 2015, all 5 of the PAEDS participating hospitals were approved by their respective Human Research Ethics Committees to operate under a waiver of consent model for surveillance of all conditions. Surveillance nurses collected detailed clinical information from the medical records and vaccination history from the Australian Childhood Immunisation Register (ACIR). 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 1).

Conditions under surveillance

In 2015, there were 6 conditions under surveillance at all PAEDS sites: acute flaccid paralysis (AFP), acute childhood encephalitis (ACE), intussusception (IS), pertussis, and varicella-zoster virus infection (VZV; varicella and herpes zoster). Surveillance for influenza (in collaboration with FluCAN) was undertaken at 2 PAEDS sites: CHW (Sydney) and PMH (Perth).

In addition, in 2015, data collected from surveillance of 2 select PAEDS conditions in children aged <5 years, AFP and ACE, were analysed monthly to identify any serious acute neurologic events (SANE) that occurred within 6 weeks of receipt of a seasonal influenza vaccine.

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 2 stool samples for enteric virus identification by the National Enterovirus Reference Laboratory (NERL) in Melbourne as part of the Global Polio Eradication Initiative (GPEI).[3,4] For other conditions, samples are collected for virus genotyping (e.g. VZV) or for additional pathogen testing (e.g. ACE).

Quality assurance and ICD-10-AM audits

To check for completeness of case ascertainment, PAEDS nurses at each site conducted regular retrospective audits of medical records by searching for primary and secondary ICD-10-AM codes describing the relevant conditions (e.g. K56.1 for IS). Cases ascertained through the medical records 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.[1] As an additional quality assurance measure, periodic audits were undertaken by investigators of case medical records to assess accuracy of data collected.

Data management

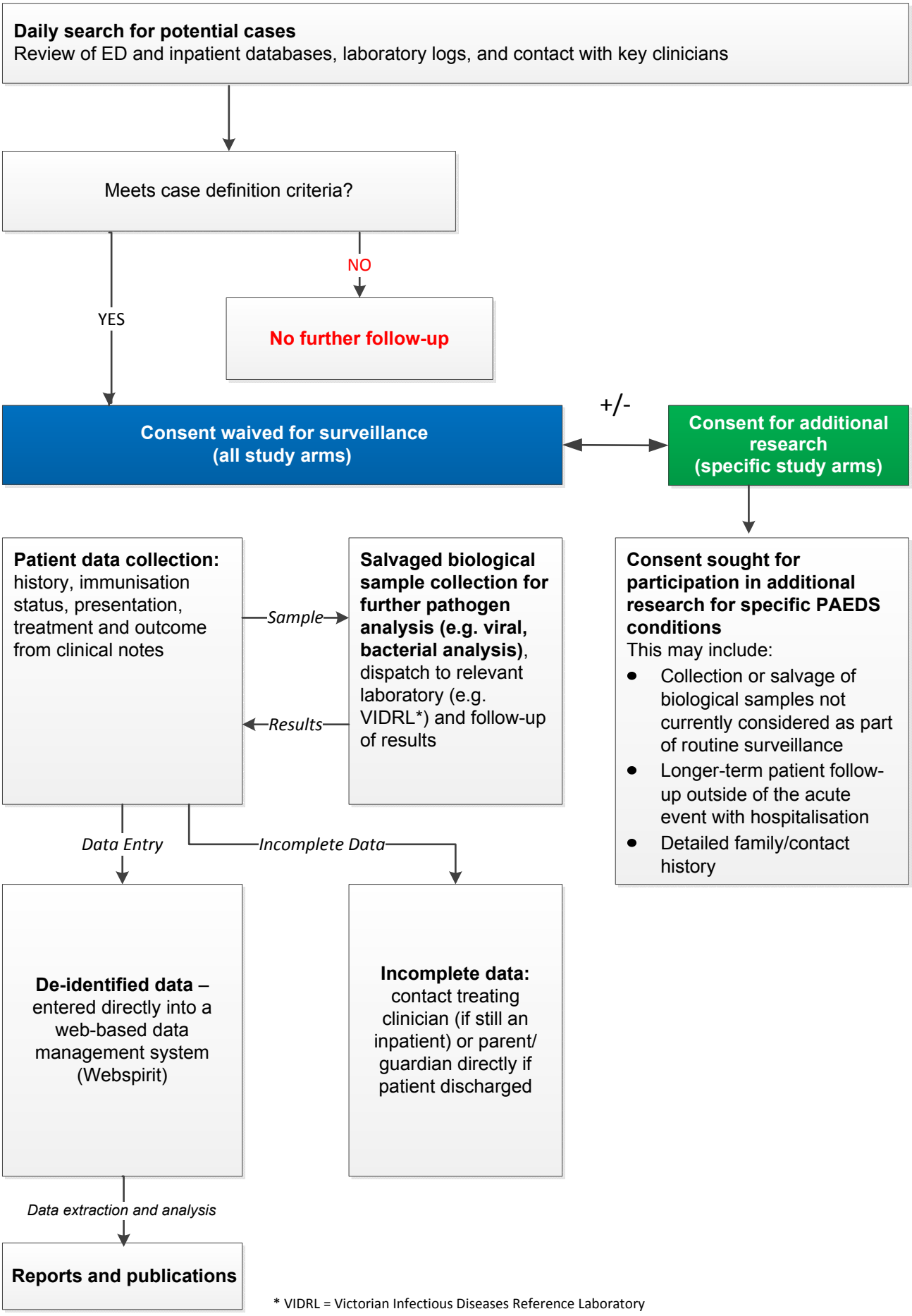
PAEDS utilises a web-based data management system called 'WebSpirit'[5] which enables online data entry by surveillance nurses at each site and centralised data extraction. Data is held securely and exported on a regular basis by staff at the PAEDS coordinating centre for clinical review, monthly quality checks, analysis and reporting.[1]

Table 1: PAEDS conditions under surveillance, case definitions and rationale, 2015

Condition and case definition	Rationale
Acute flaccid paralysis (AFP) *Case definition:* Any child aged 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.	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 1/100,000 cases per year. Data collected on AFP also contributes to separate analysis for SANE*.
Acute childhood encephalitis (ACE) *Case definition:* Any child aged birth to <15 years **AND** hospitalised with acute encephalopathy **AND** who has one or more of the following: fever, seizures, focal neurological findings, at least one abnormality of cerebrospinal fluid, or EEG/ neuroimaging findings consistent with infection-related encephalitis.	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 is 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.[6] Data collected on ACE also contributes to separate analysis for SANE*.
Influenza – FluCAN *(Seasonally: April–October)* Case definition: Any hospitalised child aged birth to <18 years who presents with suspected influenza (respiratory symptoms +/– fever) who is influenza PCR-positive.	The emergence of H1N1-09 influenza in 2009 demonstrated the importance of enhanced influenza surveillance in children.[7] PAEDS provides unique timely sentinel data from 2 sites (Sydney and Perth) on influenza hospitalisations, including complications and deaths, which can be used to inform public health response and policy. The data on children supplements 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.
Intussusception (IS) *Case definition:* 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.[8]	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).[9] Surveillance also aims to describe the epidemiology, aetiology and severity of IS.[10,11]
Pertussis *Case definition:* Any child aged birth to <15 years admitted to hospital with laboratory-confirmed pertussis.	Despite immunisation coverage approaching 93%, pertussis continues to cause significant morbidity and mortality, particularly in very young Australian children.[12] 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. This surveillance data will assist in optimising pertussis prevention strategies.
Varicella–Zoster Virus Infection *Case definition:* Any child aged birth to <15 years hospitalised for varicella or herpes zoster with or without complications.	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.[13] 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.

*SANE – Serious acute neurological event

Figure 1: PAEDS method for surveillance using the waiver of consent model plus opt-in consent for additional research of specific study arms



* VIDRL = Victorian Infectious Diseases Reference Laboratory

Results

In 2015, there were 164,932 admissions at the 5 participating PAEDS sites (Table 2). This represents a substantial proportion of all hospitalisations to specialist paediatric centres in Australia.[1]

There were 674 cases identified across all PAEDS conditions under surveillance and sites in 2015 (Table 3). Data on an additional 215 control cases (influenza test-negative ARI cases) were collected under FluCAN surveillance. Thus, the total number of PAEDS-reported cases (excluding influenza test-negative controls) between the network's inception in 2007 and 31 December 2015 was 4,897.

Surveillance results for 2015

Table 3 shows case numbers for all 6 conditions in 2015 and details of auditing and ICD-coded hospital discharge data.

Acute flaccid paralysis

PAEDS reported 46 cases of AFP to the NERL in 2015, meeting the 1/100,000 surveillance target in children aged <15 years (estimated Australian population in this age group is 4.48 million[14]). Stools could not be collected from 2 of 46 cases due to *Clostridium botulinum* infection. Of the remaining 44 cases, at least 1 stool sample was collected within 2 weeks of onset of paralysis for 29 cases (66%), and 2 stool samples were collected for 11 cases (25%). The most common diagnoses associated with AFP were Guillain-

Table 2: Total hospital admissions and ED presentations (inclusive of admitted patients) for the 5 hospitals participating in PAEDS in 2015

PAEDS site	Hospital admissions	ED presentations	Total cases all conditions (% hospital admissions)*
CHW, Sydney	32,224	57,562	213 (0.67)
RCH, Melbourne	45,427	86,842	89 (0.20)
WCH, Adelaide	21,343	46,004	52 (0.24)
PMH, Perth	27,510	64,935	211 (0.77)
LCCH, Brisbane	38,428	64,345	109 (0.28)
Total	164,932	319,688	674 (0.41)

*Denominator used is hospitalisations, some intussusception, or more infrequently AFP cases, may not be included as they may be treated in ED only.

Table 3: Number of cases captured by PAEDS in 2015 by condition and method of case ascertainment

Condition	Case identification methods			
	Total cases captured by active surveillance	Number captured by PAEDS only, not ICD-coded*	Number captured retrospectively following ICD-10 audit	Total captured cases (surveillance and ICD-10 audit combined)
Acute flaccid paralysis†	45	21	1	46
Acute childhood encephalitis	209	125	15	224
Influenza‡	219	–	–	219
Intussusception	53	7	14	67
Pertussis	73	4	5	78
Varicella or Herpes Zoster	34	10	6	40
Total	633	167	41	674

* These cases did not have an ICD-10 code for this hospitalisation that was consistent with the condition diagnosed.
† AFP numbers may differ from those published in APSU and/or VIDRL reports due to differences in surveillance systems.
‡ Influenza – an additional 215 control cases were captured at CHW (Sydney) and PMH (Perth). No ICD audit was carried out on this condition.

Barré syndrome (GBS; 39%), acute demyelinating encephalomyelitis (ADEM; 17%) and transverse myelitis (13%).

Acute childhood encephalitis

PAEDS identified 224 cases of suspected ACE in 2015. Among these cases was a cluster of *Mycoplasma pneumoniae* encephalitis in NSW that was reported to local public health authorities. A subsequent outbreak investigation was undertaken with the Western Sydney local public health unit and the NSW Ministry of Health rapid surveillance team to which NSW ACE investigators contributed (manuscript under review). Additionally, a signal of increased suspected encephalitis associated with parechovirus was identified in NSW during October 2015. This was communicated to public health authorities in 3 states (NSW, Queensland and Victoria) showing increased case numbers and included advice for clinicians regarding case management. The majority of children with ACE were recruited to follow-up studies and have had biological specimens salvaged for future analysis.

Serious acute neurological events (SANE) following immunisation

Vaccine data from AFP and ACE surveillance was reviewed in combination and included an additional 29 children aged <2 years hospitalised with ICD-coded febrile seizures (FS) from CHW (ascertained through separately funded FS surveillance). During 2015, 68 SANE in children aged <5 years were identified (24 confirmed and 9 probable encephalitis, 5 GBS and 1 ADEM). Only 4 of the 68 children (6%) had received an influenza vaccine; one had been vaccinated within 42 days of symptom onset. This was a previously well child who developed acute encephalitis 18 days following an influenza vaccine but was found to have a viral infection (HHV6) as a likely cause of the encephalitis.

Influenza

There were 219 children with confirmed influenza admitted to CHW (n=98) and PMH (n=121) in the 2015 season (April – October), and 215 influenza test-negative controls were enrolled. Of the cases, 16 (7.3%) were admitted to the intensive care unit, and 108 (49%) had chronic co-morbidities. Of the 202 children with influenza where vaccination status was ascertained, 24 (12%) were vaccinated.

Intussusception

Of the 67 cases of IS identified, 37 (55%) met level 1 Brighton Criteria.[8] Of the affected children, 9 (24%) had received a rotavirus vaccine in the previous 21 days: none had IS within 21 days after their first dose of vaccine, 3 had IS within 21 days after their second dose, and 6 had IS within 21 days after their third dose. Three (33%) of the 9 children required surgery to correct the IS and 6 (67%) children were successfully treated with air enema. Among all 37 cases of level 1 IS, 13 (35%) children required surgery and 24 (65%) resolved following air enema.

Pertussis

There were 78 children hospitalised with laboratory-confirmed pertussis in 2015. Nine children (12%) required admission to the intensive care unit. Of all children, approximately 42% (n=33) were under 3 months of age. A preliminary analysis of data from 2012 (when surveillance commenced) to 2015 showed that, among children aged <1 year (n=180), 37% (n=66) of cases were in infants <6 weeks of age (vaccine ineligible), 30 (16.7%) children required ICU admission, and 11 children (6.1%) required assisted ventilation. One death occurred in an infant <1 month old.[15]

Varicella and Herpes Zoster

In 2015, 40 cases of varicella-zoster virus infection were identified (27 varicella; 13 herpes zoster). Of these, vesicular fluid or vesicle scraping samples were obtained from 14 (35%); in many children sampling was difficult as vesicles had crusted over by the time the child was identified. Of the 40 children, 18 (45%) were eligible for NIP-funded varicella vaccination but only 14 had been vaccinated.

Discussion

PAEDS provides novel and unique data on hospitalisations due to selected uncommon serious childhood conditions, particularly VPDs and potential AEFI. Active case finding by specialist surveillance nurses and collection of detailed clinical and laboratory information provides comprehensive and timely data not available from other surveillance systems. The waiver of consent framework for surveillance allows vitally important information to be captured from otherwise hard-to-reach groups, such as those who are critically ill, lost to follow-up, or from a non-English speaking background (NESB), thereby obtaining more complete data from the broader population. Quality assurance processes such as ICD-10-AM audits, periodic case reviews and improved data management have enhanced both the yield and quality of the data captured.

PAEDS surveillance for AFP continues to provide the majority of cases for national surveillance, enabling Australia to meet the WHO AFP surveillance target for 2015.[3] Achieving the WHO stool collection target of 2 stool samples within 2 weeks remains challenging in the context of a modern health system where a non-polio AFP diagnosis is rapidly available[16]; however, PAEDS nurses facilitated collection of at least 1 stool sample in 64% of PAEDS AFP cases ascertained in 2015.

PAEDS encephalitis surveillance is realising its potential to support early detection of epidemic infectious diseases in children. In addition, arising out of the surveillance is the largest cohort of all-cause childhood encephalitis cases in the world that will be used to define the contemporary causes and consequences of this challenging condition. To date ACE surveillance has identified the importance of emerging infectious pathogens such as parechovirus and enterovirus 71,[17,18] defined the contribution of seasonal influenza to ACE,[19] and contributed data to support the development of clinical guidelines for encephalitis in Australia and New Zealand.[20,21]

Table 4. Table of Acronyms

ACE	Acute Childhood Encephalitis
ACIR	Australian Childhood Immunisation Register
ADEM	Acute Demyelinating Encephalomyelitis
AEFI	Adverse events following immunisation
AFP	Acute Flaccid Paralysis
APSU	Australian Paediatric Surveillance Unit
ARI	Acute Respiratory Illness
CHW	The Children's Hospital at Westmead
ED	Emergency department
FluCAN	Influenza Complications Alert Network
FS	Febrile Seizures
GBS	Guillain Barre Syndrome
GPEI	Global Polio Eradication Initiative
ICD	International Classification of Diseases
IS	Intussusception
LCCH	Lady Cilento Children's Hospital Brisbane
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
PMH	Princess Margaret Hospital Perth
RCH	The Royal Children's Hospital Melbourne
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 Organisation

Surveillance of serious acute neurological events following influenza vaccination offers confidence in the influenza vaccines of 2015. Although case numbers were small, there was no indication of an association between influenza vaccine and the onset of serious neurologic disease. Data from multiple influenza seasons could strengthen this preliminary finding, and future studies could potentially include examination of such events temporally associated with other vaccines, such as pertussis booster vaccination.

PAEDS contributes important paediatric data to national influenza surveillance in collaboration with FluCAN.[22] PAEDS data highlights the need for improved uptake of influenza vaccination in children, particularly those who have predisposing chronic conditions.[22] The influenza season of 2015 saw an increase in cases of influenza type B disease.[23] Availability of quadrivalent vaccines under the NIP schedule from 2016[24] may help to address this burden. With influenza vaccines changing each year to provide optimal coverage against new strains, ongoing surveillance is critical to understanding disease burden and how vaccination strategies can be best targeted. A limitation of the PAEDS FluCAN surveillance was that only two sites (WA and NSW) were included in 2015. The future aim is to include all jurisdictions in paediatric influenza surveillance.

PAEDS data has been instrumental in identifying an association between IS and rotavirus vaccine when given as the first dose to children aged 1–3 months.[9] In light of this documented but low vaccine-associated risk, IS surveillance continues. Analysis of the >500 IS cases for which PAEDS holds detailed clinical data is underway to compare the clinical characteristics of vaccine proximate cases with non-vaccine proximate cases.

Pertussis continues to be one of the least well controlled VPDs in Australia.[15] Infants too young for vaccination, or those for whom vaccination is delayed, are at the highest risk of severe morbidity and mortality.[12,25] Sole reliance on cocooning strategies is no longer the primary recommendation for prevention of pertussis transmission to young infants. Since 2015, early infant protection via maternal vaccination during each pregnancy has been recommended.[25-27]

PAEDS data for 2007–2014 showed that 78% of children hospitalised with varicella or herpes zoster were unimmunised.[13] In 2015, vaccine uptake in the eligible age group was slightly increased (78% vs 64%).[1] This surveillance provides the only nationally consistent, verified source of data for severe varicella and herpes zoster, enabling ongoing evaluation of varicella vaccination under the NIP. Analysis of this data to determine varicella vaccine effectiveness is underway.

Currently, PAEDS operates in 5 tertiary paediatric hospitals based in large metropolitan centres, limiting surveillance coverage to populations served by these hospitals. Despite this, we estimate that a substantial proportion of all paediatric admissions to tertiary paediatric services are covered by PAEDS.[1] From late 2016, PAEDS, under an NHMRC partnership grant (ID1113851), expanded to include two new hospital sites, Royal Darwin Hospital in the Northern Territory and Monash Children's Hospital in Victoria. Under the grant, PAEDS activity also expanded to use captured cases to conduct detailed research into vaccine uptake, vaccine effectiveness, and knowledge and attitudes of families of children hospitalised with influenza and pertussis, with the aim of developing improved strategies to better protect young infants.

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. This unique surveillance platform also has the potential to be used for other urgent or research-focused studies for which active surveillance is optimal. More information on PAEDS is available at www.paeds.edu.au.

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