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## **Paediatric Active Enhanced Disease Surveillance (PAEDS) 2017 and 2018: Prospective hospital-based surveillance for serious paediatric conditions**

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Kristine K Macartney on behalf of the PAEDS network

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# Paediatric Active Enhanced Disease Surveillance (PAEDS) 2017 and 2018: Prospective hospital-based surveillance for serious paediatric conditions

Jocelynn E McRae, Helen E Quinn, Gemma L Saravanos, Samantha J Carlson, Philip N Britton, Nigel W Crawford, Nicholas J Wood, Helen S Marshall and Kristine K Macartney on behalf of the PAEDS network

## 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). This report presents surveillance data for 2017 and 2018.

### Methods

Specialist nurses screened hospital admissions, emergency department (ED) 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. In 2017 and 2018 these included 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. An additional social research component was added to evaluate parental attitudes to vaccination.

### Results

PAEDS captured 1,571 and 923 cases for 2017 and 2018, respectively, across all conditions under surveillance. Key outcomes of PAEDS included: contribution to national AFP surveillance to reach the World Health Organization reporting targets; identification of a third human parechovirus outbreak among other infectious diseases linked to ACE; demonstration of variable influenza activity between 2017 and 2018, with vaccine effectiveness (VE) analysis demonstrating that the protection offered through vaccination is season-dependent. All IS cases associated with vaccine receipt were reported to the relevant state health department. Varicella and herpes zoster case numbers remained unchanged, with vaccine uptake found to be suboptimal among eligible children under the NIP. Enhanced pertussis surveillance continues to capture controls for VE estimation. Surveillance for invasive meningococcal disease showed predominance for serotype B at 57% over 2 years among 77 cases where serotyping was available, and surveillance for invasive group A streptococcus captured severe disease in children.

## Conclusions

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

## Introduction

This is the fourth annual report of the Paediatric Active Enhanced Disease Surveillance (PAEDS) network and summarises data collected in 2017 and 2018. PAEDS data, including impact and outcomes of previous years, can be found in earlier reports.<sup>1-3</sup>

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 the select conditions under surveillance. In some instances, emergency department (ED) presentations are also included. PAEDS data are 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 importance. PAEDS is better positioned to adequately capture timely and comprehensive data compared with other surveillance programs that are usually unable to do so.<sup>4</sup>

During 2017, the PAEDS network expanded from five to 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, formerly Princess Margaret Hospital), Perth, Western Australia; and Queensland Children's Hospital (QCH, formerly Lady Cilento Children's Hospital), Brisbane, Queensland; with the addition of Royal Darwin Hospital (RDH), Darwin, Northern Territory and Monash Children's Hospital, Melbourne, Victoria. All sites remained active with PAEDS in 2018. 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 participating state/territory 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. 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 medical, laboratory and nursing staff.<sup>1,2</sup>

For both 2017 and 2018 all seven participating hospitals were approved by their respective Human Research Ethics Committees to operate under a waiver of consent model for condition surveillance, with most hospitals engaged in all conditions of interest for 2017. 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

**Table 1: PAEDS conditions under surveillance, case definitions and rationale, 2017 and 2018**

Condition and case definition	Rationale
<p><b>Acute flaccid paralysis (AFP)</b>  <i>Case definition:</i>                      Any child aged from birth to &lt; 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 &lt; 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 &lt; 15 years. Data collected on AFP also contributes to separate analysis for SANE.<sup>a</sup></p>
<p><b>Acute childhood encephalitis (ACE)</b>  <i>Case definition:</i>                      Any child aged from birth to &lt; 15 years <b>AND</b> hospitalised with acute encephalopathy <b>AND</b> 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 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.<sup>8</sup> Data collected on ACE also contributes to separate analysis for SANE.<sup>a</sup></p>
<p><b>Influenza – FluCAN (Seasonally: April–October)</b>  <i>Case definition:</i>                      Any child aged from birth to &lt; 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.<sup>9</sup> PAEDS provides unique timely sentinel data from 6 sites 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 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.</p>
<p><b>Intussusception (IS)</b>  <i>Case definition:</i>                      Any child aged &lt; 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.<sup>10</sup></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).<sup>11</sup> Surveillance also aims to describe the epidemiology, aetiology and severity of IS.<sup>12,13</sup></p>
<p><b>Pertussis</b>  <i>Case definition:</i>  <u>Hospitalised pertussis</u> – Any child aged from birth to &lt; 15 years hospitalised with laboratory-confirmed pertussis.  <u>Pertussis vaccine effectiveness study</u> – Any child aged from birth to &lt; 6 months with laboratory-confirmed pertussis identified from either the “Hospitalised Pertussis” study (above) or from the emergency department.</p>	<p>Despite immunisation coverage approaching 93%, pertussis continues to cause significant morbidity and mortality, particularly in very young Australian children.<sup>14</sup> 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 comorbidities 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 &lt; 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

**Varicella–zoster virus (VZV) Infection***Case definition:*

Any child aged from 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.<sup>15</sup> 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.

**Invasive meningococcal disease (IMD)***Case definition:*

Any child aged from birth to < 18 years who is hospitalised with laboratory-confirmed invasive meningococcal disease.

Invasive Meningococcal Disease (IMD) causes death in young healthy children and adolescents in 5–10% of cases.<sup>16–18</sup> 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.<sup>19–21</sup> 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.

**Invasive group A streptococcus (IGAS)***Case definition:*

Any child aged from birth to < 18 years hospitalised with laboratory-confirmed invasive group A streptococcus disease.

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%.<sup>22,23</sup> 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.

**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

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%.<sup>24</sup> 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 is to understand attitudes about and access to influenza vaccination experienced by parents of children hospitalised for influenza.

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 2017 and 2018, there were six conditions under surveillance at all PAEDS sites: acute flaccid paralysis (AFP), intussusception (IS), pertussis, varicella-zoster virus infection (VZV; varicella and herpes zoster), invasive meningococcal disease (IMD); and invasive group A streptococcus (IGAS). Surveillance for influenza (in collaboration with FluCAN) was expanded from two to six PAEDS sites in 2017: CHW (Sydney), PCH (Perth), WCH (Adelaide), LCCH (Brisbane), RDH (Darwin) and MCH (Melbourne) which commenced surveillance in August. In April 2018, RCH (Melbourne) also commenced influenza surveillance. Acute childhood encephalitis (ACE) surveillance was conducted by all sites except RDH (Darwin) and MCH (Melbourne). From 2017 a social research component was added that involved interviewing parents of children admitted with influenza or pertussis. In addition, data collected from surveillance of two 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 two stool samples for enteric virus identification by the National Enterovirus Reference Laboratory (NERL) in Melbourne as part of the Global Polio Eradication Initiative.<sup>5,6</sup> For other conditions,

samples were collected for virus genotyping (e.g. VZV) or for additional pathogen characterisation (e.g. ACE, IGAS).

### Quality assurance and ICD-10-AM audits

To check for completeness of case ascertainment, PAEDS nurses at each site conducted regular retrospective audits of hospitalisation records 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. As an additional quality assurance measure, periodic audits were undertaken by investigators of case medical records to assess accuracy of data collected.

### Data management

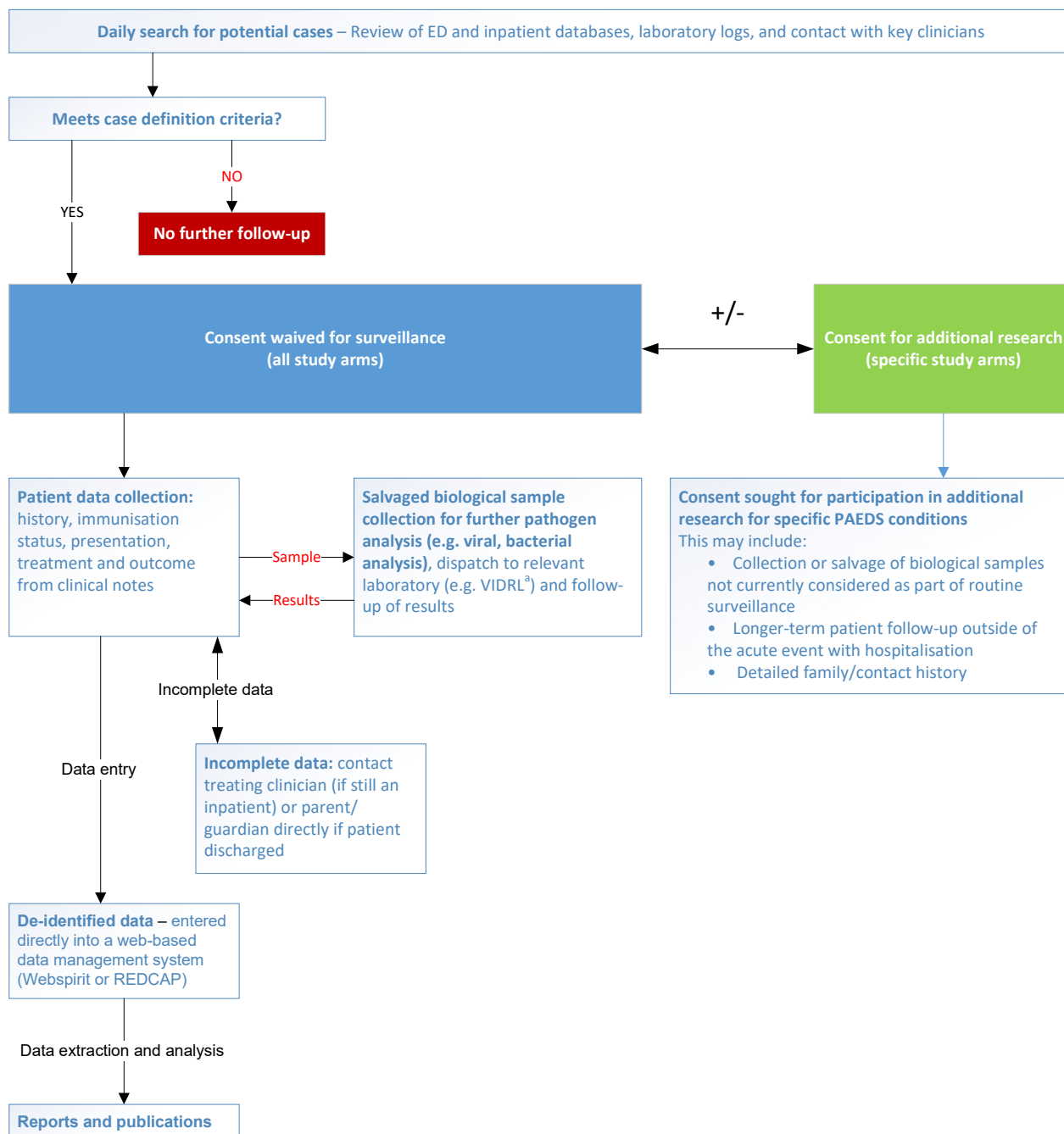
PAEDS utilises a web-based data management system called 'WebSpirit',<sup>7</sup> which enables online data entry by surveillance nurses at each site and centralised data extraction. Data are held securely and exported on a regular basis by staff at the PAEDS coordinating centre for clinical review, monthly quality checks, analysis and reporting. Data for two specific study arms — FluCAN and IGAS — are also recorded on a separate secure system, REDCAP.

### Results

In 2017, there were 206,031 admissions at the seven participating PAEDS sites (Table 2a). There were 1,571 cases identified across all PAEDS conditions under surveillance and sites in 2017 (Table 3a). Data on an additional 887 control cases (influenza test-negative controls) were collected under FluCAN surveillance and a further 100 test-negative controls for the pertussis vaccine effectiveness study.

In 2018, there were 207,560 admissions at the seven participating PAEDS sites (Table 2b). There were 923 cases identified across all PAEDS

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



a VIDRL = Victorian Infectious Diseases Reference Laboratory



**Table 2a: Total hospital admissions and ED presentations (including admitted patients) for the seven hospitals participating in PAEDS in 2017**

2017			
PAEDS site	Hospital admissions	ED presentations	Total PAEDS cases all conditions (% hospital admissions) <sup>a</sup>
CHW, Sydney	51,158	92,662	351 (0.7)
RCH, Melbourne <sup>b</sup>	49,169	86,347	113 (0.2)
WCH, Adelaide	21,169	47,233	341 (1.6)
PCH, Perth	27,452	61,924	167 (0.6)
LCCH, Brisbane	25,998	70,951	457 (1.8)
RDH, Darwin	30,29	15,630	32 (1.0)
MCH, Melbourne <sup>b</sup>	28,056	68,317	110 (0.4)
<b>Total</b>	<b>206,031</b>	<b>443,064</b>	<b>1,571 (0.8)</b>

**Table 2b: Total hospital admissions and ED presentations (including admitted patients) for the seven hospitals participating in PAEDS in 2018**

2018			
PAEDS site	Hospital admissions	ED presentations	Total PAEDS cases all conditions (% hospital admissions) <sup>a</sup>
CHW, Sydney	50,170	98,074	216 (0.4)
RCH, Melbourne <sup>b</sup>	51,639	84,774	179 (0.3)
WCH, Adelaide	22,155	44,867	97 (0.4)
PCH, Perth	26,893	62,985	150 (0.6)
LCCH, Brisbane	24,717	70,461	169 (0.7)
RDH, Darwin	2,751	14,627	24 (0.9)
MCH, Melbourne <sup>b</sup>	29,235	66,582	88 (0.3)
<b>Total</b>	<b>207,560</b>	<b>442,370</b>	<b>923 (0.4)</b>

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

b MCH commenced influenza surveillance in August 2017; RCH commenced influenza surveillance in April 2018.

conditions under surveillance and sites in 2018 (Table 3b). Data on an additional 424 control cases (influenza test-negative controls) were collected under FluCAN surveillance and a further 65 test-negative controls for the pertussis vaccine effectiveness study.

Since the inception of PAEDS in 2007 a total of 8,064 cases (excluding controls) have been recruited.

## Surveillance results for 2017 and 2018

Tables 3a and 3b show the case numbers for all 8 conditions per year and details of auditing and ICD-coded hospital discharge data.

### Acute flaccid paralysis

Summary data of notifications to the NERL are based on date of AFP symptom onset (as opposed to date of admission reported in Tables 3a and 3b). PAEDS reported 51 cases of AFP in 2017 and 49 cases in 2018 to the NERL, meeting the surveillance target of 1 non-polio AFP case per 100,000 children aged < 15 years for both years<sup>5</sup> (estimated Australian population in this age group – 4.64 million in 2017 and 4.70 million in 2018).<sup>25, 26</sup> Of the 51 cases in 2017, at least 1 stool sample was collected within 2 weeks of onset of paralysis for 28 cases (55%), and 2 stool samples were collected for 20 cases (39%). The most common diagnoses associated with AFP were Guillain-Barré syndrome (GBS; 41%), transverse myelitis (25%) and acute demyelinating encephalomyelitis (ADEM; 6%).

Of the 49 AFP cases in 2018, at least 1 stool sample was collected within 2 weeks of onset of paralysis for 35 cases (71%), and 2 stool samples were collected for 23 cases (47%). The most common diagnoses associated with AFP were Guillain-Barré syndrome (GBS; 39%), transverse myelitis (20%) and acute demyelinating encephalomyelitis (ADEM; 8%).

As part of SANE, vaccine-proximate cases were clinically reviewed and any that were deemed plausibly consistent with an AEFI were reported

via existing channels. In 2017, three cases were reported; of these, one had documented receipt of influenza, and all cases reported receipt of other vaccine types. In 2018, six vaccine-proximate cases were reported; of these three had documented receipt of influenza while the other three reported receipt of other vaccine types.

### Acute childhood encephalitis

PAEDS identified a total of 332 cases of suspected ACE, comprising 189 cases from 2017 and 143 from 2018. The month of August 2017 recorded the highest number of cases (27, 8.1%).

Parechovirus was detected in the cerebrospinal fluid (CSF) of 32 cases (9.6%) presenting between March 2017 and January 2018, with the highest frequency of cases reported in November 2017 (9, 28.1%). Other viral pathogens frequently detected in CSF included enterovirus (32, 9.6%) and herpes simplex virus (7, 2.1%). Bacterial-meningo-encephalitis was confirmed in 12 (3.6%) cases, and the most frequent pathogens detected were group B streptococcus (4, 33.3%) and *Streptococcus pneumoniae* (3, 25.0%). *Neisseria meningitidis* (serogroup B) and *Mycobacterium tuberculosis* were each detected in one case. Influenza virus was detected in 23 (6.9%) cases, with the highest frequency observed between August and October 2017.

Following clinical review, 13 suspected ACE cases were assessed as plausibly consistent with an AEFI and were reported via existing channels.<sup>27</sup> Of these, four cases had documented receipt of a proximate influenza vaccine, of which two had also received other vaccine types.

### Influenza

In the 2017 season (April–October), 1,027 children were hospitalised with laboratory-confirmed influenza across the PAEDS network: CHW (n = 254), WCH (n = 264), PCH (n = 66), QCH (n = 324), RDH (n = 21) and MH (n = 98). Of these children, 116 were aged < 6 months, 459 were aged between 6 months and < 5 years and 452 were aged > 5 years. Influenza A was

Table 3a: Number of cases captured by PAEDS in 2017 by condition and method of case ascertainment

Condition	2017				Total captured cases (surveillance and ICD-10 audit combined)
	Case identification methods			Number captured retrospectively following ICD-10 audit	
	Total cases captured by active surveillance	Number captured by PAEDS only, not ICD-coded <sup>a</sup>	Number captured retrospectively following ICD-10 audit		
Acute flaccid paralysis <sup>b</sup>	47	20	3	50	
Acute childhood encephalitis	177	84	12	189	
Influenza <sup>c,d</sup>	1,027	–	–	1,027	
Intussusception	51	1	6	57	
Pertussis	64	9	0	64	
Varicella or herpes zoster	38	7	2	40	
Invasive meningococcal disease	38	2	0	38	
Invasive group A streptococcus	101	29	5	106	
<b>Total</b>	<b>1,543</b>	<b>152</b>	<b>28</b>	<b>1,571</b>	

a These cases did not have an ICD-10 code for this hospitalisation that was consistent with the condition diagnosed.

b AFP numbers above are based on date of admission. Total number of cases for the year discussed below differ as they are based on date of symptom onset. In this report, one case had a symptom onset date of 31 December 2017 but was not admitted until 18 January 2018.

c Influenza – an additional 886 control cases were captured for 2017 by the PAEDS network participating sites.

d No ICD audit was carried out on these conditions due to high impact on resources.

Table 3b: Number of cases captured by PAEDS in 2018 by condition and method of case ascertainment

Condition	2018				Total captured cases (surveillance and ICD-10 audit combined)
	Total cases captured by active surveillance	Case identification methods		Number captured retrospectively following ICD-10 audit	
		Number captured by PAEDS only, not ICD-coded <sup>a</sup>	Number captured by PAEDS only, not ICD-coded <sup>a</sup>		
Acute flaccid paralysis <sup>b</sup>	49	22	1	1	50
Acute childhood encephalitis <sup>d</sup>	143	-	-	-	143
Influenza <sup>c,d</sup>	424	-	-	-	424
Intussusception	47	4	6	6	53
Pertussis	44	8	0	0	44
Varicella or herpes zoster	45	13	2	2	47
Invasive meningococcal disease	53	4	0	0	53
Invasive group A streptococcus <sup>d</sup>	109	-	-	-	109
<b>Total</b>	<b>914</b>	<b>51</b>	<b>9</b>	<b>9</b>	<b>923</b>

a These cases did not have an ICD-10 code for this hospitalisation that was consistent with the condition diagnosed.  
b AFP numbers above are based on date of admission. Total number of cases for the year discussed below differ as they are based on date of symptom onset. In this report, one case had a symptom onset date of 31 December 2017 but was not admitted until 18 January 2018.  
c Influenza – an additional 886 and 426 control cases were captured for 2017 and 2018 respectively by the PAEDS network participating sites.  
d No ICD audit was carried out on these conditions due to high impact on resources.

detected among 674 (66%) cases and Influenza B among 338 (33%) cases; 12 (1%) cases had multiple types detected; 3 (0.3%) cases had no subtype reported. In addition, 887 influenza test-negative controls were enrolled to calculate vaccine effectiveness. Of all influenza confirmed cases where data was complete, 496/1025 (48%) had underlying medical conditions, 156/1025 (15%) were admitted to the intensive care unit and 6/1023 (0.6%) deaths were identified. Influenza vaccine uptake among cases was reported for 58/432 (13%) children aged between 6 months and < 5 years and 66/423 (16%) children aged > 5 years. Among infant cases aged < 6 months maternal vaccination status was ascertained in 86 paired mothers, with 36 (42%) being vaccinated for influenza. Among controls, vaccine uptake was reported for 62/426 (15%) children aged between 6 months and < 5 years and 34/129 (26%) children aged > 5 years. Among infant controls aged < 6 months maternal vaccination status was ascertained in 166 mothers. Of these, 66 (40%) were vaccinated during their pregnancy.

In the 2018 season (April–October), 424 children were hospitalised with laboratory-confirmed influenza across the PAEDS network: CHW (n = 109), RCH (n = 65), WCH (n = 52), PCH (n = 73), QCH (n = 57), RDH (n = 12) and MH (n = 56). Of these children, 37 were aged < 6 months, 219 children were aged between 6 months and < 5 years and 168 were aged > 5 years. Influenza A was detected among 386 (91%) cases and Influenza B among 37 (9%) cases. In addition, 424 influenza test-negative controls were enrolled to calculate vaccine effectiveness. Of all influenza confirmed cases, 175/424 (41%) had underlying medical conditions, 41/424 (10%) were admitted to the intensive care unit and 2/424 (0.5%) deaths were identified. Influenza vaccine uptake among cases was reported for 19/209 (9%) children aged between 6 months and < 5 years and 24/159 (15%) children aged > 5 years. Among infant cases aged < 6 months maternal vaccination status was ascertained in 33 paired mothers, with 8 (24%) being vaccinated for influenza. Among controls, vaccine uptake was reported for 82/240 (34%) children aged between 6 months and < 5 years and 26/57 (46%) children aged > 5

years. Among infant controls aged < 6 months maternal vaccination status was ascertained in 100 mothers. Of these, 56 (56%) were vaccinated during their pregnancy.

### **Intussusception**

In 2017, 57 cases of IS were identified, of which 44 (77%) met level 1 Brighton criteria.<sup>10</sup> Six (14%) had received a rotavirus vaccine in the preceding 21 days from intussusception: three following the first dose of vaccine, one after their second dose and two after their third dose. Among all 44 cases of level 1 IS, 11 (25%) children required surgery and 33 (75%) resolved following air/hydrostatic enema. Of the six children who had IS within 21 days of vaccination, one (17%) required surgery (aged 18 weeks) to correct the IS and 5 (83%) children were successfully treated with air/hydrostatic enema. There were no deaths.

In 2018, 53 cases of IS were identified, of which 38 (72%) met level 1 Brighton criteria.<sup>10</sup> Four (11%) cases had received a rotavirus vaccine in the preceding 21 days from intussusception; all cases occurred following the second dose of the vaccine. Among all 38 cases of level 1 IS, 10 (26%) children required surgery and 28 (74%) resolved following air/hydrostatic enema. Of the four children who had IS within 21 days of vaccination, two (50%) required surgery (ages 20 and 21 weeks) to correct the IS and the remaining two (50%) children were successfully treated with air/hydrostatic enema. There were no deaths.

### **Pertussis**

In 2017, 64 children were hospitalised with laboratory-confirmed pertussis across the PAEDS network. Eleven children (17%) required admission to the intensive care unit; 73% (n = 8) of these admissions were for infants < 3 months of age. For the adjunct vaccine effectiveness study, 34 infant cases aged < 6 months were enrolled in the year, together with 100 control infants.

In 2018, there were 44 children who presented to hospital with laboratory-confirmed pertussis.

Four children (9%) required admission to the intensive care unit; 3 of these 4 admissions were for infants < 2 months of age. For the adjunct vaccine effectiveness study, 24 infant cases aged < 6 months were enrolled in the year, together with 65 control infants.

### **Varicella and herpes zoster**

In 2017, 40 cases of varicella-zoster virus infection were identified (31 varicella; 9 herpes zoster) across the PAEDS network. Vesicular fluid or vesicle scraping samples were obtained from 28 (70%) of these children. Of the 40 children, 26 (65%) were eligible for NIP-funded varicella vaccination; where vaccination status was ascertained, only 17/24 (71%) had been vaccinated.

In 2018, 47 cases of varicella-zoster virus infection were identified (37 varicella; 10 herpes zoster) across the PAEDS network. Vesicular fluid or vesicle scraping samples were obtained from 29 (63%) of these children. Of the 47 children, 35 (75%) were eligible for NIP-funded varicella vaccination; where vaccination status was ascertained, only 23/34 (68%) had been vaccinated.

### **Invasive meningococcal disease**

In 2017, 38 cases of IMD were identified across the PAEDS network. Thirty-two (84%) cases were aged < 5 years, of which 22 (69%) were < 12 months of age. Six (16%) cases were aged between 5 and 15 years, and none of them was older than 15 years. Serogroup B was the predominating strain with 16 cases overall; 14 (88%) of these were in children aged < 5 years. Serogroups W and Y were identified in 11 and 2 cases, respectively; for nine cases serogroup/genotype could not be determined. All children were of eligible age for vaccination, with 20 (53%) children vaccinated for meningococcal C through monovalent or combination vaccines and three (8%) children vaccinated for serogroups A, C, W-135 and Y through quadrivalent vaccine. No child had been vaccinated for meningococcal B. Nineteen cases (50%) exhibited meningitis on presentation and 19 (50%) were septicaemic. Eight of these children had both meningitis and septicaemia.

The most common reported symptoms on presentation were fever 35 (92%), lethargy 33 (86%), vomiting 28 (74%), irritability 24 (63%), unwell appearance 25 (66%), rash 22 (58%) and refusal to eat or drink 22 (58%). Mortality was reported for one case in South Australia.

In 2018, 53 cases of IMD were identified across the PAEDS network. Thirty-eight (72%) cases were aged < 5 years, of which 20 (53%) were < 12 months of age. Ten (19%) cases were aged between 5 and 15 years, and 5 were aged > 15 years. Serogroup B was the predominating strain with 28 cases overall; 18 (64%) of these were in children aged < 5 years. Serogroups W and Y were identified in 18 and 2 cases, respectively; for five cases serogroup/genotype could not be determined. All but one child (aged less than 6 weeks) were of eligible age for vaccination, with 26 (49%) vaccinated for meningococcal C through monovalent or combination vaccines and six (11%) children vaccinated for serogroups A, C, W-135 and Y through quadrivalent vaccine. No child had been vaccinated for meningococcal B disease. Thirty-one (58%) exhibited meningitis on presentation and 30 (57%) were septicaemic. Fourteen of these children had both meningitis and septicaemia. The most common reported symptoms on presentation were fever 50 (94%), lethargy 42 (81%), refusal to eat or drink 39 (75%), irritability 38 (73%), unwell appearance 38 (72%), vomiting 34 (64%) and rash 30 (58%). Mortality was reported for one case in New South Wales.

### **Invasive group A streptococcus**

Surveillance for IGAS disease cases admitted to sentinel PAEDS sites was undertaken between 2017 and 2018. Data analysed and reported here is for the period 1 July 2016 to 30 June 2018. In addition to hospital data, PAEDS surveillance teams contacted these patients 6 months after discharge to assess longer-term outcomes. In total 181 children with a median age of 2.9 years (range 7 days to 16 years) were enrolled. There was a male predominance (59.1%) in cases, and 21 (11.6%) children were Aboriginal or Torres Strait Islander. The principal site of invasive

infection was the blood (126 children, 69.6%), but the most frequent clinical presentation was pneumonia in 46 children (25.4%). Twenty-six children developed streptococcal toxic shock syndrome (14.4%), and 74 had severe disease (40.9%), including 71 admitted to the intensive care unit. Five children died (2.8%). There was no association between disease severity and age, sex or Aboriginal and Torres Strait Islander status. Of 81 patients with emm-typing results, 18 different strains were identified; 61 (75.3%) were emm-1, -4 or -12. Prophylaxis was reportedly offered to 85 patients' contacts (47.0%). At discharge and 6 months, 29.3% and 15.2% of the children had persisting health problems, respectively.

### Social research

In 2017, 27 parents of children hospitalised for laboratory-confirmed influenza in New South Wales and South Australia were interviewed. Questions were guided by the Social Ecological Model (SEM), exploring all levels of influence on vaccination uptake. Transcripts were thematically analysed. Themes were categorised into the components of the Capability-Opportunity-Motivation-Behaviour (COM-B) model. The themes regarding barriers to influenza vaccination were 1) Limited Capability – misinterpretations and knowledge gaps; 2) Lack of Opportunity – inconvenient vaccination pathway, missing recommendations, absence of promotion to all and the social norm; and 3) Missing Motivation – hierarchy of perceived seriousness, safety concerns, a preference for 'natural' ways.<sup>28</sup>

The themes from these interviews, as well as modified questions from other studies, were used to develop a survey to understand parents' access to and attitudes about influenza vaccination. The survey was piloted at sites in New South Wales, South Australia, Victoria, Queensland and the Northern Territory from July to October 2018. 75 parents (39%) responded. Only 28% of the parents of 69 children aged  $\geq 6$  months recalled receiving an influenza vaccination recommendation from a healthcare provider, despite 81%

**Table 4. Table of acronyms**

Acronym	Description
<b>ACE</b>	Acute Childhood Encephalitis
<b>ADEM</b>	Acute Demyelinating Encephalomyelitis
<b>AEFI</b>	Adverse Events Following Immunisation
<b>AFP</b>	Acute Flaccid Paralysis
<b>AIR</b>	Australian Immunisation Register
<b>APSU</b>	Australian Paediatric Surveillance Unit
<b>ARI</b>	Acute Respiratory Illness
<b>CHW</b>	The Children's Hospital at Westmead
<b>ED</b>	Emergency department
<b>FluCAN</b>	Influenza Complications Alert Network
<b>FS</b>	Febrile Seizures
<b>GBS</b>	Guillain–Barré Syndrome
<b>ICD</b>	International Classification of Diseases
<b>IMD</b>	Invasive Meningococcal Disease
<b>IGAS</b>	Invasive Group A Streptococcus
<b>IS</b>	Intussusception
<b>LCCH</b>	Lady Cilento Children's Hospital Brisbane
<b>NCIRS</b>	National Centre for Immunisation Research and Surveillance
<b>NERL</b>	National Enterovirus Reference Laboratory
<b>NESB</b>	Non-English Speaking Background
<b>NHMRC</b>	National Health and Medical Research Council
<b>NIP</b>	National Immunisation Program
<b>NSW</b>	New South Wales
<b>PAEDS</b>	Paediatric Active Enhanced Disease Surveillance
<b>PMH</b>	Princess Margaret Hospital Perth
<b>RCH</b>	The Royal Children's Hospital Melbourne
<b>SANE</b>	Serious Acute Neurological Event
<b>VE</b>	Vaccine Effectiveness
<b>VIDRL</b>	Victorian Infectious Diseases Reference Laboratory
<b>VPD</b>	Vaccine-Preventable Diseases
<b>VZV</b>	Varicella Zoster Virus
<b>WCH</b>	The Women's and Children's Hospital Adelaide
<b>WHO</b>	World Health Organization

having taken their child to a general practitioner at least twice in the previous 12 months. Few (12%) were vaccinated prior to hospitalisation. Overall, most parents did not report difficulties in accessing influenza vaccination, but parents of vaccinated children reported easier access. Many parents (69%, 41/59) had some degree of hesitancy about influenza vaccination. There was no significant difference between the median scores of specific influenza vaccine concerns between parents of vaccinated and unvaccinated children. One third (32%, 21/65) were undecided about future influenza vaccination – many stated a discussion with a healthcare provider about influenza vaccine safety and efficacy was required to assist with their decision.

## Discussion

PAEDS, now in operation for more than 10 years, continues to provide novel and unique data on hospitalisations due to uncommon serious childhood conditions, particularly VPDs and potential AEFI. By the end of 2017 and throughout 2018, PAEDS was operational across seven tertiary paediatric hospitals based in large metropolitan centres. Active case finding by specialist surveillance nurses and collection of detailed clinical and laboratory information provide comprehensive and timely data not available from other surveillance systems. Surveillance was undertaken for eight conditions with an additional social research component funded by an NHMRC partnership grant (ID1113851) and added to better understand attitudes and behaviours among parents around vaccination.

PAEDS surveillance for AFP continues to provide the majority of cases for national surveillance, enabling Australia to meet the WHO AFP surveillance target for 2017 and 2018.<sup>5</sup> Achieving the WHO stool collection target of two stool samples within 2 weeks remains challenging in the context of a modern health system where a non-polio AFP diagnosis is common;<sup>29</sup> however, PAEDS nurses facilitated collection of at least one stool sample in 55% of cases in 2017 and 71% in 2018. PAEDS continues to make enhanced efforts to educate clinical staff to improve aware-

ness of the need for public health monitoring of AFP and associated biological specimen requirements for national surveillance.

PAEDS encephalitis surveillance continues to support early detection of epidemic infectious diseases in children, and associated pathogens observed during this period were consistent with previously described infectious causes of childhood encephalitis.<sup>27</sup> PAEDS detection, and notification of a third national HPeV3 outbreak in 2017–2018, emphasises the value of ACE surveillance.<sup>29</sup> Furthermore, PAEDS documentation of the burden of influenza-associated neurological disease, particularly in otherwise-well children aged < 5 years, supported funded vaccine programs aimed at influenza prevention in this age group.<sup>30</sup> These severe, albeit rare, manifestations of paediatric influenza should be monitored as part of program evaluation. PAEDS-ACE investigators are currently seeking to continue ACE surveillance, but to reduce the burden of detailed data collection for research and improve efficiency of case review and reporting.

PAEDS continues to contribute important paediatric data to national influenza surveillance in collaboration with FluCAN and with support of an NHMRC partnership grant (ID1113851).<sup>31</sup> Influenza vaccines are adjusted each year to provide optimal coverage against circulating influenza strains, so ongoing surveillance is critical to understanding disease burden, to maximise vaccine efficacy and to evaluate vaccination program strategies. In 2017, record influenza activity was observed across most states and territories with figures not seen since the 2009 influenza pandemic.<sup>32</sup> Lesser activity was seen in WA.<sup>32</sup> PAEDS influenza surveillance in 2017 was conducted with the addition of four sites, enhancing national data on paediatric hospitalisations as reported through FluCAN. Vaccine coverage among all PAEDS test-negative controls aged > 6 months was low at 17% and point estimates of vaccine effectiveness using combined PAEDS-FluCAN data incorporating additional paediatric data from other hospitals was 30.3% (95%CI: 2.6%; 50.2%).<sup>31</sup> Maternal vaccine uptake among controls was low at 40% and point estimates of



maternal vaccine protection against hospitalisation of infants aged < 6 months was low at 11% but suggestive of moderate protection (53%, 95%CI: -39%; 84%) for infants aged < 8 weeks.<sup>33</sup> Predominance of influenza A (H3N2), associated poor vaccine effectiveness against this strain and low vaccine coverage would have contributed to such a high-activity influenza season.

In 2018, the seventh PAEDS site joined influenza surveillance. Overall activity for the year across Australia was starkly different from that in 2017, with activity observed to be lower than that in recent years.<sup>34</sup> Following the 2017 season, new state- and territory-funded influenza vaccination programs were introduced in ACT, NSW, Qld, Vic, SA and Tas for children and infants aged 6 months to < 5 years.<sup>35</sup> Among this age group, and across the PAEDS network (including NT and WA), vaccine uptake was 34% and higher again (46%) among children > 5 years. Maternal vaccine uptake among test-negative control infants aged < 6 months had also notably improved to 56%, above that reported for 2017. Continued effort is needed to emphasise the importance of vaccination among all ages, especially for at-risk groups, as influenza seasons remain unpredictable. Point estimates of vaccine effectiveness for 2018 among children aged > 6 months was reportedly 78.8% (95%CI: 66.9%; 86.4%),<sup>36</sup> and analysis of maternal vaccine effectiveness against hospitalisation in infants aged < 6 months is underway. These estimates are in keeping with a season predominated by influenza A H1N1 where the vaccine is known to be more protective than for other strains.<sup>34</sup> Continued surveillance and timely reporting of paediatric influenza hospitalisation data is important to inform policy and practice on immunisation programs impacting all Australian children.

PAEDS data have been instrumental in quantifying the association between IS and rotavirus vaccine when given to infants.<sup>11–13</sup> Given the documented but low vaccine-associated risk, IS surveillance continues. Analysis of the > 300 Brighton level 1 IS cases aged < 9 months for which PAEDS holds detailed clinical data is underway to compare the clinical charac-

teristics of vaccine-proximate cases with non-vaccine-proximate cases. Preliminary results indicate that IS is more severe (needing longer hospitalisation, surgery or ICU admission) in younger infants (aged < 14 weeks) than older infants; however, there was no difference in severity between vaccine-proximate IS cases and idiopathic cases.

Despite vaccination, pertussis remains endemic in Australia with epidemics occurring every 3–4 years.<sup>37</sup> Infants too young for vaccination, or those for whom vaccination is delayed, are at the highest risk of severe morbidity and mortality.<sup>14,38</sup> Since 2015, early infant protection via maternal vaccination during each pregnancy has been recommended.<sup>38–40</sup> The expansion of the pertussis surveillance in 2016, through an NHMRC partnership grant (ID1113851) to collect controls and undertake maternal vaccine effectiveness analysis, will provide an important contribution in understanding the role of this strategy in the Australian context.

PAEDS VZV case numbers remained steady over 2017 and 2018, and slightly lower than case numbers in 2016.<sup>3</sup> Current vaccine uptake in eligible children remains suboptimal at 68%, a slight increase on previous years (2016, 60%; 2015, 64%).<sup>1,3</sup> Despite a moderate VE, Australia's program has impacted on VZV disease burden. Continued surveillance through the PAEDS network provides the only nationally consistent, verified source of data for severe VZV disease, which enables ongoing evaluation of varicella vaccination with the introduction of the quadrivalent MMRV vaccine under the NIP.

Clinical features and outcomes of meningococcal disease are not captured in adequate detail in current IMD surveillance programs. PAEDS offers the ability to monitor changes in clinical presentation and sequelae which may relate to changes in the epidemiology of disease such as with the recent increase in serogroup W disease in Australia. Nationally, Men ACWY vaccination is available for 1-year-olds and many states have now introduced meningococcal ACWY vaccine programs for adolescents. Monitoring

the impact of these programs, including severity of disease and any vaccine failures, is an important priority.

For the period July 2016 – June 2018, PAEDS surveillance revealed a high frequency of severe IGAS disease among children, resulting in complex and prolonged treatment, followed by longer-term sequelae for many patients. A correlation with the seasonal burden of influenza was noted. There is potential for influenza vaccination to minimise the risk of IGAS and co-infection, prior to IGAS vaccines being developed. The PAEDS study is the first to assess the outcome of IGAS disease in children at discharge and at 6 months, with 15% of the cohort having ongoing health issues as a result of their infection. This important study provides further impetus for establishing a national surveillance system for IGAS disease in children and adults in Australia. In addition to optimising clinical management of IGAS disease, there is a need to closely monitor the epidemiology of this condition. PAEDS is examining the rates of contact prophylaxis administration to mitigate household contacts infection risk.

Influenza social research, supported by an NHMRC partnership grant (ID1113851), has enabled identification of many parents who had not received a positive recommendation from a healthcare provider to vaccinate their child. This is one of the key facilitators of influenza vaccination of children in Australia,<sup>41–45</sup> likely because a presumptive recommendation is seen as an endorsement and also provides the opportunity to discuss any concern.<sup>46</sup> To assist healthcare providers in their ability to vaccinate patients, strategies such as provider education, electronic prompts, standing order protocols and incorporating influenza vaccination into routine care should be prioritised.<sup>47,48</sup> In addition to this, a commitment to continuing to improve parents' access to influenza vaccination is important.

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. In 2018, PAEDS undertook a program evaluation to comprehensively look into the deliverables and operations of the surveillance system, enabling future planning and system improvements. In 2019, plans are in progress to improve timely data reporting and quality processes. Quality assurance processes such as ICD-10-AM audits, periodic case reviews and data management continue to enhance both the yield and the quality of the data captured.

The PAEDS network stands as a unique surveillance platform that 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.org.au](http://www.paeds.org.au).

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