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Australian Paediatric Surveillance Unit (APSU) Annual Surveillance Report 2020

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Australian Paediatric Surveillance Unit (APSU) Annual Surveillance Report 2020

Suzy M Teutsch, Carlos A Nunez, Anne Morris, Guy D Eslick, Gulam Khandaker, Angela Berkhout, Daniel Novakovic, Julia ML Brotherton, Skye McGregor, Jonathan King, Ece Egilmezer, Robert Booy, Cheryl A Jones, William Rawlinson, Bruce R Thorley and Elizabeth J Elliott

Abstract

For 27 years, national prospective data on selected rare childhood diseases have been collected monthly by the Australian Paediatric Surveillance Unit (APSU) from paediatricians and other clinical specialists who report cases in children aged up to 16 years. We report here the annual results of APSU surveillance in 2020 for ten rare communicable diseases and complications of communicable diseases, namely: acute flaccid paralysis (AFP); congenital cytomegalovirus (CMV) infection; neonatal herpes simplex virus (HSV) infection; perinatal exposure to human immunodeficiency virus (HIV); paediatric HIV infection; severe complications of seasonal influenza; juvenile onset recurrent respiratory papillomatosis (JoRRP); congenital rubella syndrome; congenital varicella syndrome; and neonatal varicella infection. We describe the results for each disease in the context of the total period of study, including demographics, clinical characteristics, treatment and short-term outcomes. Despite challenges presented by the coronavirus disease 2019 (COVID-19) pandemic in 2020, more than 1,400 paediatricians reported regularly to the APSU and an overall monthly reporting rate of > 90% was achieved. The minimum AFP target of 1 case per 100,000 children aged less than 15 years was achieved and there were few cases of vaccine-preventable diseases (JoRRP, rubella, varicella). However, high cases of congenital CMV, neonatal HSV and perinatal exposure to HIV persist. There were no severe complications of seasonal influenza reported for the first time in 13 years. This is consistent with other surveillance data reporting a decline of influenza and other communicable diseases in 2020, and likely reflects the wider effects of public health measures to reduce transmission of SARS-CoV-2 in the Australian community.

Keywords: Australia, child, communicable disease, public health surveillance, rare disease

Introduction

Since 1993, the Australian Paediatric Surveillance Unit (APSU) has facilitated national prospective surveillance of selected rare childhood diseases and other rare health conditions. Each month, demographic, clinical, treatment and outcome data are collected from paediatricians and other health professionals on relevant children aged less than 16 years. Conditions under APSU surveillance include communicable and non-communicable diseases. APSU data have influenced policy, prevention and management of rare diseases. The APSU surveillance

system has been evaluated^{1,2} and found to be timely, flexible, and representative of paediatric practice nationally. It is valued by Australian paediatricians for the low workload and ease of reporting, and for providing opportunities to improve their knowledge of rare diseases and to contribute to translational research.² Key characteristics of the APSU include: the large database of paediatricians representing each state/territory and working in both urban and regional/remote settings; the ease of prospective monthly reporting for paediatricians; the availability of online data capture; and access to the surveillance mechanism for multiple research

groups.³ Importantly, the APSU has the flexibility to rapidly add new studies of rare diseases of emerging importance, for example H1N1pdm09 virus infection during the 2009 influenza pandemic;⁴ juvenile onset recurrent respiratory papillomatosis caused by human papillomavirus;⁵ and microcephaly in the context of an international outbreak of Zika virus infection.⁶

In this report, we describe the results of APSU surveillance conducted in 2020 for ten communicable diseases and complications of communicable diseases in the context of ongoing surveillance as a whole.

Surveillance method

Between 1 January and 31 December 2020, a report card listing between 14 and 16 rare diseases in children was distributed each month, either by email (95.2%) or as a reply-paid paper card (4.8%), to 1,430 paediatricians and other clinicians located across Australia. These clinicians consisted of those who were registered with the APSU as 'contributors' and were considered to be 'active' (i.e. they worked with children in a clinical setting and had agreed to report to the APSU). Paediatricians who work exclusively in research, administration or public health are not considered active. An example (September 2020) report card is shown in Figure 1. The conditions listed can be categorised as either rare communicable diseases or complications of rare communicable diseases, rare genetic disorders, uncommon injuries, or adverse drug reaction or prenatal alcohol exposure.

Upon receiving the monthly report card, APSU contributors are asked to indicate on the card whether they had seen a child newly diagnosed within the previous month with one or more of the diseases or conditions listed. If they have not seen a case, they return the card indicating 'nothing to report'. If they have seen a case, they indicate this on the card. Clinicians who notify a case are then sent a link and asked to complete a clinical case report form (CRF) electronically using the secure REDCap data capture system or via paper format. A link to the CRF is also included on the electronic report card to enable simultaneous reporting and

completion of the CRF. All data collected are identified and entered into a secure database for cleaning and storage.

In 2020, ten of the conditions under APSU surveillance and listed on the report card were rare communicable diseases or complications of rare communicable diseases. They were: acute flaccid paralysis (AFP); congenital cytomegalovirus infection (cCMV); neonatal herpes simplex virus infection (HSV); perinatal exposure to human immunodeficiency virus (HIV) infection; paediatric HIV infection; severe complications of seasonal influenza, including co-infection with SARS-CoV-2 (i.e. Coronavirus disease; COVID-19); juvenile onset recurrent respiratory papillomatosis (JoRRP); congenital rubella syndrome (CRS); congenital varicella syndrome (CVS); and neonatal varicella infection.

Minimum incidence estimates for 2020 and for the whole study period for each condition were calculated by dividing the number of cases reported to the APSU by the relevant population total of children, according to the Australian Bureau of Statistics (ABS)⁷ or the Australian Institute of Health and Welfare (AIHW),⁸ either less than 15 years (AFP, severe complications of influenza, JoRRP),⁷ less than 16 years (paediatric HIV)⁷ or live births (cCMV, HSV, perinatal exposure to HIV, CRS, CVS and neonatal varicella).⁸ Incidence estimates were expressed as per 100,000 persons per annum and 95% confidence intervals (95% CI) were calculated for each incidence estimate.

Results

Representativeness of reporting and response rates

In 2020, there were 1,430 clinicians (1,351 paediatricians and 79 other specialists), who were Fellows of the Royal Australasian College of Physicians (or equivalent), reporting to the APSU ('APSU contributors').

Figure 1: Example APSU monthly report card in 2020

APSU REPORT CARD: SEPTEMBER 2020B

NOTHING TO REPORT? Please select reply and type 'NTR' in the subject line of this email.

If you are reporting a **NOTIFICATION** for any condition under surveillance, please include the condition being notified, the patient's initials and date of birth in your reply email. We will use this information to improve the management of notified cases.

STUDY ALERTS

Severe Complications of Influenza: 2020 seasonal surveillance for the Commonwealth Department of Health is now closing. Please ensure all outstanding case reports are returned to APSU as soon as possible. Cases diagnosed between 1 May 2020 and 30 September 2020 and not yet notified to APSU can still be reported. Case report forms can be filled out [ONLINE](#) by following [this link](#), a printable PDF version is available by following [this link](#).

Acute Flaccid Paralysis (AFP): Please note that the AFP Case Report Form has been revised. The new form is now available for completing [ONLINE](#) by following [this link](#). A printable version of the form is available by following [this link](#).

DO YOU HAVE A CASE TO REPORT? Please complete case report forms ONLINE by selecting the relevant study link in the table below - or return the printed and completed Case Report Form(s) to the APSU (scan and email to SCHN-APSU@health.nsw.gov.au).

If you report a case, please record patient details for later reference

NEWLY DIAGNOSED CASES ONLY - Please report cases diagnosed within study period only

Study case report forms and online case report forms are available through the hyperlinks below or via the APSU website <http://apsu.org.au/studies/current/>

No of Cases	Case Report Forms – link to PRINTABLE PDF form (please return by email or fax)	ONLINE Case Report Forms – secure link to complete form ONLINE
[]	Acute flaccid paralysis **	Online Acute flaccid paralysis
[]	Montelukast and Neuropsychiatric Events	Online Montelukast and Neuropsychiatric Events
[]	Severe Complications of Influenza in Children < 15 Years Admitted to Hospital	Online Severe Complications of Influenza in Children < 15 Years Admitted to Hospital
[]	Severe Indoor Trampoline Park Injury Admitted to Hospital	Online Severe Indoor Trampoline Park Injury Admitted to Hospital
[]	Severe Injury Related to Disc Battery	Online Severe Injury Related to Disc Battery
[]	Fetal Alcohol Spectrum Disorder	Online Fetal Alcohol Spectrum Disorder
[]	MFCP2 Duplication Syndrome	
[]	Juvenile onset Recurrent Respiratory Papillomatosis	
[]	Congenital varicella	Online Congenital Varicella
[]	Neonatal varicella	Online Neonatal Varicella
[]	Rett syndrome	
[]	Congenital cytomegalovirus infection – NSW – Other States	
[]	Neonatal Herpes Simplex Virus Infection	Online Herpes Simplex Virus Infection
[]	HIV Infection and Perinatal Exposure to HIV in Australia – Mother – Child	Online HIV Infection and Perinatal Exposure to HIV in Australia – Mother – Child
[]	Congenital rubella	Online Congenital Rubella

See your protocol sheet for details regarding stool/serum specimens.

Please ALSO report cases of acute flaccid paralysis immediately by telephone to the National Enterovirus Reference Laboratory on (03) 9342 9607 or email enterovirus@mh.org.au

One-third of APSU contributors were general paediatricians and the remainder worked in a range of other sub-specialties (Figure 2).

APSU contributors worked in all Australian states and territories, in metropolitan, rural and remote locations, and in inpatient and out-patient clinical settings. There are likely gaps in coverage in geographically-isolated areas known to be poorly serviced by paediatricians and other specialists. In 2020, the proportion of paediatricians who responded from each state and territory correlated approximately with the proportion of resident children aged less than 15 years (Table 1).

The overall return rate by paediatricians of the monthly APSU report card was 91%, which included case notifications and “nothing to report” responses. In comparison, the response rate was 92% in 2019 and has been approximately 90% or greater per annum for 27 years (Figure 3).

Conditions under surveillance

Table 2 lists the ten communicable diseases under surveillance in 2020 and summarises the number of notifications received and categorisations. The case definitions for each condition studied are included in Appendix A, Table A.1.

A total of 223 notifications were received by the APSU, of which 140 were confirmed as incident cases in 2020. A total of 27 duplicate reports were also received, demonstrating the effectiveness of the APSU reporting mechanism to capture cases.

Table 3 shows the commencement year of each APSU surveillance study, the total number of confirmed cases to date, and an estimate of minimum incidence for 2020 and for the entire study period.

Acute flaccid paralysis (AFP)

AFP surveillance contributes to the Australian government’s commitment to reporting to the World Health Organization (WHO) to monitor polio-free status in the Western Pacific Region.^{9,10} In Australia, suspected cases of AFP in children aged less than 15 years are reported via these complementary surveillance mechanisms: APSU, or directly to the National Enterovirus Reference Laboratory (NERL) using the APSU clinical case report form (APSU/NERL) or by the Paediatric Active Enhanced Disease Surveillance (PAEDS) network. In July 2020, the APSU/NERL reporting mechanism transitioned from using a paper-based case report form to an online version, in order to improve timeliness and ease of reporting clinical information. All data are collated by NERL for

Figure 2: Distribution of paediatricians (n = 1,351) contributing to the APSU in 2020 by specialty

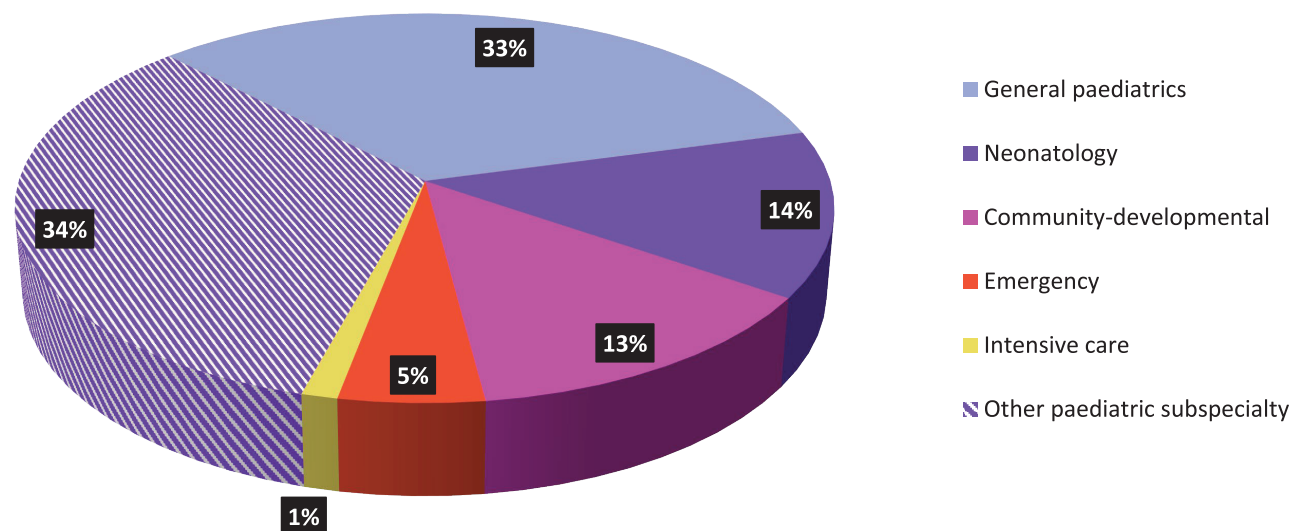


Table 1: Number and proportion of APSU contributors (n = 1,430) and of the child population aged 0–14 years in 2020 nationally, and in each Australian state and territory⁷

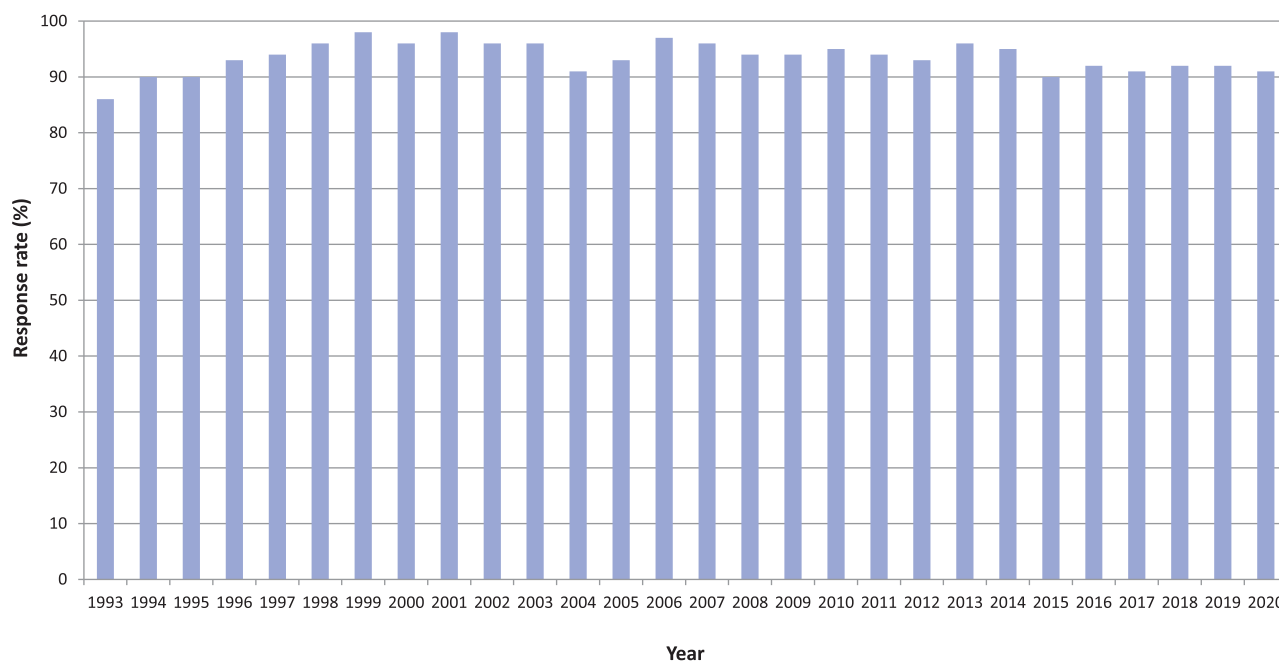
APSU contributors N = 1,430	N (%) contributors	Total child population 0–14 years in 2020	% of child population 0–14 years in 2020
New South Wales (NSW)			
Paediatricians	498 (34.8%)	1,509,265	31.6
Other specialties	37 (2.6%)		
Victoria (VIC)			
Paediatricians	330 (23.1%)	1,216,321	25.4
Other specialties	15 (1.0%)		
Queensland (QLD)			
Paediatricians	232 (16.2%)	999,268	20.9
Other specialties	9 (0.6%)		
Western Australia (WA)			
Paediatricians	142 (9.9%)	517,381	10.8
Other specialties	6 (0.4%)		
South Australia (SA)			
Paediatricians	85 (5.9%)	310,041	6.5
Other specialties	5 (0.3%)		
Tasmania (TAS)			
Paediatricians	27 (1.9%)	94,289	2.0
Other specialties	2 (0.1%)		
Australian Capital territory (ACT)			
Paediatricians	20 (1.4%)	82,775	1.7
Other specialties	5 (0.3%)		
Northern Territory (NT)			
Paediatricians	17 (1.2%)	52,525	1.1
Other specialties	0 (0%)		
Australia			
Paediatricians	1,351 (94.5%)	4,781,865	100
Other specialties^a	79 (5.5%)		

a Other specialties include: public health medicine, surgery, psychiatry, anaesthetics, general practice, nuclear medicine, obstetrics, sexual health medicine.

reporting to the Polio Expert Panel (PEP) for classification as polio, polio-compatible, non-polio AFP or non-AFP, and then to the WHO.¹¹ WHO targets for surveillance systems include a minimum of 1 non-polio AFP case per 100,000 children aged less than 15 years in the population per annum, and two stool samples collected at least 24 hours apart, within 14 days after the onset of paralysis in $\geq 80\%$ of AFP cases.¹²

In 2020, all 51 confirmed AFP cases were classified by the PEP as non-polio AFP. Australia's non-polio AFP rate was therefore 1.09 per 100,000, meeting the WHO reporting target. Adequate stool samples were collected from 32 of the 51 (63%) non-polio AFP cases.

Figure 3: Response rate of monthly report cards to APSU 1993–2020



Twenty-one of the 51 confirmed non-polio AFP cases (Table 1) were reported in New South Wales, 13 in Queensland, 12 in Victoria, two in South Australia, two in Western Australia and one in the Northern Territory. There were no cases reported in Tasmania or the Australian Capital Territory. Three cases occurred in Aboriginal and Torres Strait Islander (hereafter respectfully referred to as Indigenous) children.

A total of 26 AFP notifications were received by the APSU/NERL surveillance mechanism. Of these, 18 cases were confirmed as non-polio AFP in children less than 15 years of age; duplicate notifications were received through APSU/NERL for two cases; and six cases were classified as errors, as they either involved patients greater than 14 years of age or were later classified as non-AFP. Duplicate reports are considered indicative of good ascertainment and 12 non-polio AFP cases were reported by both the APSU/NERL and PAEDS systems. In addition, seven AFP cases (six confirmed as non-polio AFP) were reported by paediatricians via APSU/NERL who work outside the eight hospitals where PAEDS operates and would not otherwise have been detected using PAEDS alone.

The most common causes of non-polio AFP in 2020 were Guillain-Barré syndrome (GBS) and

transverse myelitis (TM). Of the 51 confirmed cases, 11 were classified with GBS (22%) and 11 with TM (22%). There were also four cases (8%) of acute disseminated encephalomyelitis (ADEM), three cases (6%) of focal mononeuropathy and three cases (6%) of demyelinating disease, broadly similar to previous years.^{3,13}

Since AFP surveillance commenced 25 years ago, a total of 1,183 cases have been confirmed by the PEP. The case rate has consistently remained ≥ 1 per 100,000 children aged <15 years each year since 2008, contributing to Australia's polio-free status.¹⁴

A 2020 review by Bao et al. outlined the joint efforts of the APSU, NERL and PAEDS AFP surveillance systems in monitoring Australia's polio-free status, in the broader context of efforts to eradicate polio globally.¹⁵ The increasing contribution of variant enteroviruses to polio-like AFP disease was highlighted.¹⁵ AFP data were published in the NERL 2015–2019 annual reports^{14,16–19} and in the PAEDS 2017–2018 report.²⁰ Australian AFP data were published fortnightly by the WHO Regional Office for the Western Pacific in the Polio Bulletin 2020⁹ and contributed to the WHO's Annual progress report on sustaining polio-free status in the Western Pacific Region.²¹

Table 2: Notifications received in 2020 of communicable diseases and complications of communicable diseases under surveillance by the APSU and their categorisation

Disease or complication under surveillance	Total notifications	Confirmed cases	Duplicates	Errors ^a	Other ^b
Acute flaccid paralysis ^c	71	51	13	7	0
Congenital cytomegalovirus	43	37	2	4	0
Neonatal herpes simplex virus infection	16	8	8	0	0
Perinatal exposure to HIV	80	43	4	0	33
Paediatric HIV infection	11	0	0	0	11
Severe complications of influenza	0	0	0	0	0
Juvenile-onset recurrent respiratory papillomatosis	1	0	0	1	0
Congenital rubella syndrome	0	0	0	0	0
Congenital varicella syndrome	1	1	0	0	0
Neonatal varicella infection	0	0	0	0	0
Total	223	140	27	12	44

a Includes administrative errors, cases outside of study definition, missing case report forms or insufficient data provided to confirm.

b Historical (prevalent) cases not previously reported.

c Includes all cases of AFP reported via the APSU/NERL and PAEDS systems. All confirmed cases have been classified by the Polio Expert Panel as 'non-polio AFP' according to World Health Organization criteria. Twenty-six cases were reported via APSU/NERL, with 18 of these cases confirmed and 12 cases duplicated by PAEDS.

Congenital cytomegalovirus (cCMV)

The APSU has conducted surveillance of cCMV infection in neonates and in infants aged up to 12 months since 1999. Congenital infection with CMV is transmitted from mother-to-child *in utero* and may present as asymptomatic or symptomatic infection in neonates. Symptoms include: prematurity, low birth weight, hearing loss or neurodevelopmental deficits.^{22,23} There are currently no vaccination regimens for the prevention of cCMV or universal antenatal screening programs for early detection of infection. However, antiviral agents including ganciclovir and valganciclovir are now recommended for the management of symptomatic cCMV infection.²⁴

In 2020, there were 35 infants classified as having definite cCMV infection, and two classified with probable cCMV infection. Cases were

aggregated to calculate an overall minimum incidence estimate of 12.10 per 100,000 births in 2020.

Of the 37 infants with confirmed cCMV (Table 1), 23 were reported in New South Wales, seven in Queensland, three in Victoria, two in Western Australia and two in the Australian Capital Territory. No cases were reported in South Australia, Tasmania or the Northern Territory.

Indigenous status was reported for 31 infants and two were Indigenous.

Twenty-eight infants were reported to be symptomatic, the most common clinical features being deafness (16), small for gestational age (8), thrombocytopenia (7) and intracranial calcification (6).

Antiviral treatment with valganciclovir or ganciclovir is currently recommended only

Table 3: Confirmed cases identified by the APSU during the period 1 January – 31 December 2020 and for the total study period, and estimated incidence per 100,000 children of the relevant population/age per annum, by condition

Communicable disease or complication of communicable disease	Surveillance study date of commencement	Confirmed cases for 1 January – 31 December 2020	Incidence estimate per 100,000 per annum and 95% CI for 2020	Confirmed cases for the whole study period to 31 December 2020	Incidence estimate per 100,000 per annum for the whole study period to 31 December 2020
Acute flaccid paralysis	March 1995	51 ^a	1.09 [0.79–1.40] ^b	1,183	1.08 [1.02–1.14] ^b
Congenital cytomegalovirus	Jan 1999	37	12.10 [8.52–16.7] ^c	399	6.34 [5.73–6.99] ^c
Neonatal herpes simplex virus	Jan 1997	8	2.62 [1.13–5.15] ^c	215	3.16 [2.76–3.61] ^c
Perinatal exposure to HIV	May 1993	43	14.06 [10.18–18.94] ^c	928	11.86 [11.11–12.65] ^c
Paediatric HIV infection	May 1993	0	0	98	0.08 [0.06–0.09] ^d
Severe complications of influenza ^e	2008 (flu season only)	0	0	695	1.20 [1.12–1.30] ^b
Juvenile-onset recurrent respiratory papillomatosis ^f	Sep 2011	0	0	17	0.04 [0.02–0.06] ^b
Congenital rubella syndrome	May 1993	0	0	54	0.69 [0.52–0.90] ^c
Congenital varicella syndrome	May 2006	1	0.33 [0.008–1.82] ^c	4	0.09 [0.02–0.23] ^c
Neonatal varicella	May 2006	0	0	31	0.68 [0.46–0.97] ^c

a Includes all cases of AFP reported via the APSU, NERL and PAEDS. All cases have been classified by the PEP as 'non-polio AFP' according to WHO criteria.

b Based on population of children aged < 15 years.⁷

c Based on number of live births.⁸

d Based on population of children aged < 16 years.⁷

e Influenza surveillance was conducted each year during the influenza season, from July to September (inclusive) for 2008 and 2010–2015; June to October (inclusive) in the 2009 H1N1 influenza pandemic year; June to September (inclusive) 2016–2019; and May to September (inclusive) in the 2020 SARS-CoV-2 coronavirus pandemic year.

f Includes both confirmed cases (visualisation on endoscopy, histological confirmation) and probable cases (visualisation on endoscopy, no histology report).

for neonates with moderate to severe cCMV symptoms, including neurological symptoms and presentation of multiple symptoms, and only for a maximum of six months.^{25,26} Of the 15/28 symptomatic infants who were eligible, all received antiviral treatment.

Outcomes were recorded for 33 infants and one infant died. This infant presented with multiple symptoms, including: encephalitis, seizures, hepatitis, hepatomegaly, jaundice, anaemia, thrombocytopenia, chorioretinitis, myocarditis, pneumonitis, splenomegaly and petechiae/purpura, and received ganciclovir treatment at diagnosis. Of the infants who survived, six had developmental delay identified within the first 12 months of age.

A symptomatic illness suggestive of maternal CMV infection was reported during pregnancy in 19 of 33 mothers (58%) for whom these data were available. CMV serology was available for 25 mothers, and all tested either immunoglobulin G (IgG) and/or IgM positive for CMV infection.

The higher frequency of confirmed cases reported in 2020 (37) compared with 2019 (15) was attributable to greater engagement between CMV study investigators and relevant paediatricians who report cases. The number of APSU contributors who reported cases in 2020 was 22 and in 2019 was 14. We believe that the greater engagement with APSU contributors in 2020 led to an overall increase in the number of contributors reporting cases and to a higher number of cases reported by individual contributors.

A total of 399 confirmed cases of cCMV have been reported to the APSU in 22 years of surveillance, with annual case numbers remaining consistent over time.²⁴

Neonatal herpes simplex virus infection (HSV)

Since 1997, the APSU has conducted surveillance for neonatal HSV in infants aged < 3 months, who have laboratory-confirmed HSV

with either symptomatic or asymptomatic infection. Symptomatic infection is either localised to specific organs, most commonly manifesting as lesions on the skin, eyes or mouth (SEM disease), or affects the central nervous system (CNS) and infants present with seizures, lethargy or irritability. Neonatal HSV may also present less commonly as disseminated infection affecting either the SEM or CNS, as well as multiple other organ systems such as the hepatic, gastrointestinal, adrenal and respiratory systems.^{27,28} Disseminated and localised CNS disease often results in devastating outcomes such as death or severe disability;²⁹⁻³¹ early treatment with acyclovir has been important in helping to ameliorate these effects.³² Primary genital herpes infection, transmitted from infected mothers to their infants, either *in utero* or shortly after birth, or exposure to an orolabial lesion, is thought to be responsible for HSV infection in infants during the neonatal period.²⁷ Maternal transmission of primary HSV infection to infants can be reduced by antiviral treatment and by continuous antiviral treatment prevent recurrences.²⁷ There is also evidence to suggest that transmission of primary HSV can be reduced by caesarean delivery.²⁷ No effective vaccine for HSV currently exists.

In 2020, eight cases of neonatal HSV were confirmed and the estimated incidence rate was 2.62 cases per 100,000 births.

Three cases were reported from Western Australia, two from Queensland, and one each from New South Wales, Victoria and the Northern Territory. There were no cases reported in South Australia, Tasmania or the Australian Capital Territory.

Indigenous status was recorded for all eight cases and one case was Indigenous.

Six cases had HSV-1 and two had HSV-2 infection.

One infant had disseminated HSV-1 disease with CNS involvement and died. Three infants had disease localised to the CNS and one of these

infants died with HSV-2 infection. Another of the infants with localised CNS disease, who survived, also had SEM disease. Three infants had SEM only. One infant was asymptomatic. All infants received antiviral treatment with intravenous acyclovir at diagnosis, including the two infants who died.

In the 24 years since APSU surveillance for neonatal HSV commenced, a total of 215 confirmed cases have been reported, with variable annual incidence. Reported case numbers were highest in 2015 (16 cases) and lowest in 2017 (two cases).

Our previous publication of APSU data³³ and more recent analysisⁱ suggest that the incidence of neonatal HSV disease may be higher in Queensland or increasing relative to other Australian states and territories. An analysis of 13 years of medical record data on neonatal HSV cases identified by laboratory confirmation in Queensland, which included APSU HSV study investigators Berkhout and Jones,³⁴ compared the incidence estimate in Queensland for 2005–2017 with our national APSU incidence estimate from 1997–2011.³³ The analysis showed that the incidence in Queensland was nearly three times greater than the national incidence estimated by the APSU.³⁴ The reasons for this apparent increase in neonatal HSV in Queensland are unclear and would require an audit of medical records from each Australian state and territory for comparison with the APSU data to determine whether or not the increase in incidence was real, or a reflection of good surveillance and greater awareness of neonatal HSV in Queensland.

In addition, we examined CNS disease with or without dissemination in 91/199 cases of neonatal HSV infection reported to the APSU between 1997 and 2019. Infants were aged less than 60 days and were symptomatic. CNS disease was caused by both HSV-1 (55%) and HSV-2 (45%) but infants with disseminated CNS disease had

a higher mortality than infants with localised CNS disease, and with infants with other forms of disseminated HSV disease.ⁱⁱ

Perinatal exposure to human immunodeficiency virus (HIV) and paediatric HIV infection

Transmission of HIV in Australia has decreased significantly in the past few decades, with increased use of condoms, treatment as prevention (TasP), pre-exposure prophylaxis (PrEP) and clean needle exchange programs.³⁵ Survival and quality of life for people living with HIV has increased following the introduction of effective antiretroviral therapy.³⁵ Although rare, infants and children remain at risk of HIV infection, most often from perinatal exposure from an infected mother and occasionally from other exposures, especially if born in a country where there is high HIV prevalence.^{35,36} In collaboration with the Kirby Institute, the APSU has conducted surveillance for both perinatal exposure of infants born to women with HIV infection and for paediatric HIV infection (either acquired via perinatal exposure or other exposures) since 1993.

Perinatal exposure to HIV

In 2020, there were 80 infants with perinatal exposure reported to the APSU, of which four were duplicates and 33 were historic cases born between 1997 and 2018 and not previously reported. These cases were identified through an audit of cases reported to the National HIV Registry at the Kirby Institute and through clinician reporting of prevalent cases. Forty-three confirmed cases were infants born in 2020 in Australia, compared with 59 cases reported in 2019,³ and 29 cases reported in 2018.¹³

Based on 43 cases, the incidence estimate of perinatal exposure for 2020 was 14.06 per 100,000 births. Eleven infants were each reported in New South Wales and Western Australia, seven in Victoria and one in the Northern Territory.

i C Jones, S Teutsch, unpublished.

ii S Teutsch et al, manuscript in preparation.

Thirteen infants did not have their place of reporting recorded. Twenty-six infants had their Indigenous status recorded and two were Indigenous.

HIV test results were available for 26/43 perinatally-exposed infants and none were positive. Test results were often not available at the time of reporting. Twenty-eight of the infants were known to have been treated with prophylactic antiviral treatment after birth.

The risk of mother-to-child transmission (MTCT) of HIV may be substantially reduced through the mother's use of antiretroviral therapy during pregnancy and antiretroviral and prophylactic treatment of the child, elective caesarean delivery if appropriate, and avoidance of breastfeeding.³⁷ Data were available for 31/43 mothers. Twenty-four (77%) were born outside Australia and three identified as Indigenous. Thirty received antiretroviral therapy during pregnancy, with these data missing for one mother. Mode of delivery was recorded for 29 mothers: 16 had a vaginal delivery, 10 had an elective caesarean and three had an emergency caesarean. Of 30 infants for whom data were available, one child was breastfed.

For the 33 historic cases with perinatal exposure, HIV test results were available for 32 cases and 23 were positive. Two of the 23 infants who were HIV positive were born in Australia and the remaining 21 infants were born overseas.

Paediatric HIV

There were no children with paediatric HIV (non-perinatal exposure) diagnosed in 2020. The 11 cases reported to the APSU in 2020 were all prevalent cases diagnosed between 2011 and 2017, ranging in age from six to 15 years, identified by an audit of cases reported to the National HIV Registry. The last time children with HIV infection were reported to the APSU was in 2014, when three children who were all born outside Australia were reported.³⁸ Ten of the 11 prevalent cases reported in 2020 were born outside Australia and one case was Indigenous.

Seven cases had an exposure in a high-prevalence country. For one case, information was missing on the source of exposure. Treatment and clinical outcomes were not recorded for the 11 historical cases.

In 28 years of surveillance, a total of 928 confirmed cases of perinatal exposure to HIV and 98 confirmed cases of paediatric HIV infection have been reported to the APSU (Table 2). A decrease in the rate of vertical transmission of HIV has been observed over time.^{35,36}

Severe complications of influenza

At the request of the Australian Government, the APSU has conducted surveillance of severe complications of laboratory-confirmed influenza virus infection in hospitalised children aged < 15 years during the Australian winter season since 2008, following an unusually high number of children hospitalised with severe influenza in 2007.^{39,40} In 2020, surveillance commenced earlier than in previous years, on 1 May, and finished on 30 September. Due to the global COVID-19 pandemic, additional questions were included in the case report form to capture information about COVID-19 co-infection in children with severe influenza.

In 2020, there were no notifications of severe complications of influenza to the APSU in any Australian state or territory. This contrasts with the 77 notifications (62 confirmed cases) reported in 2019.³ Our APSU surveillance results are consistent with reports of a marked reduction in influenza infection and severity from other surveillance systems during the 2020 influenza season.⁴¹

This is the first time in thirteen seasons of APSU surveillance that no cases have been reported. In the previous twelve seasons, a total of 695 confirmed cases had been reported. The annual number of cases had fluctuated, with the highest number reported during the 2009 H1N1 pandemic and in 2017 (106 cases in each year), and the lowest number reported in 2018 (20 cases).

In 2020, data from ten years of APSU surveillance of severe complications of influenza (2008–2017) in 613 children were published.⁴² In 613 children, 65 different complications were reported to the APSU during that period. Pneumonia was the most common complication, occurring in more than half of all cases, and accounting for 88% of all respiratory complications (Figure 4a); 30 deaths were notified in reported cases. Influenza vaccination rates were low, and more than half the children were previously healthy, indicating a need for increased access for free vaccination for all Australian children, not only children aged less than five years, Indigenous children, or children at increased risk of developing complications.⁴³

Juvenile-onset recurrent respiratory papillomatosis (JoRRP)

Recurrent respiratory papillomatosis affects the larynx and upper aerodigestive tract by way of benign tumours (papillomata) resulting from infection with human papillomavirus (HPV). The juvenile onset form (JoRRP) is thought to result from perinatal exposure to HPV (typically types 6 and 11) in the maternal genital tract. Persistent HPV infection affects epithelial cells, producing warty outgrowths which can impact normal voice function and cause airway obstruction.^{5,44,45}

Incidence surveillance of JoRRP has been conducted by the APSU since October 2011 with a network of specialist paediatric otolaryngologists around Australia contributing monthly reports and providing data on epidemiological, vaccination and treatment status of new cases as they are identified. Initial surveillance data collected between October 2011 and the end of 2016 showed a sharp decrease in JoRRP incidence following the implementation of a national HPV vaccination program in 2007, suggesting that HPV immunisation of mothers prevents development of JoRRP in children.⁵

2020 is the third consecutive year in which no incident cases of JoRRP have been reported to the APSU. A total of 17 confirmed cases had

been reported between October 2011 and the end of 2017, with the two most recent cases reported in 2017.⁴⁶

Congenital rubella syndrome (CRS)

Since 1993, APSU has conducted surveillance of CRS, in which APSU contributors are asked to notify any cases of children or adolescents aged up to 16 years who have definite or suspected CRS with defects, based on history, clinical and laboratory findings. Infants with congenital defects may be born to mothers with known or unknown rubella virus infection during pregnancy and commonly present with a rash-like illness.⁴⁷ CRS may result in serious conditions such as deafness, impaired vision, thrombocytopenia and encephalitis, and structural anomalies may affect the ear, eye, heart and liver.⁴⁷ In Australia, universal vaccination for rubella has been available for the past 50 years.⁴⁸

In 2020, there were no cases of CRS reported to the APSU in any Australian state or territory. Similarly, no cases of laboratory-identified CRS were reported in 2020 to the National Notifiable Disease Surveillance System (NNDSS). No notifications of CRS have been reported to the APSU or to the NNDSS since 2015. In 2015, there were two notifications of suspected CRS, of which one met the criteria for confirmed CRS.⁴⁹ This was an infant born in Australia to a mother who was born overseas and had not been vaccinated against rubella virus infection.

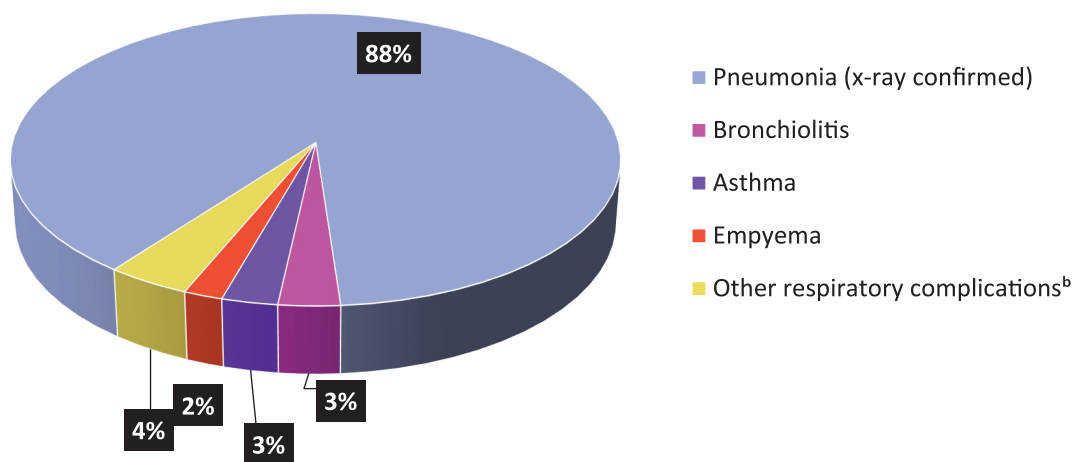
A total of 54 confirmed cases of CRS have been reported to the APSU in the 28 years since surveillance commenced. The decrease in notifications reported over time is attributed to an increase in vaccination of adolescents and of infants.⁵⁰

Congenital varicella syndrome (CVS) and neonatal varicella infection

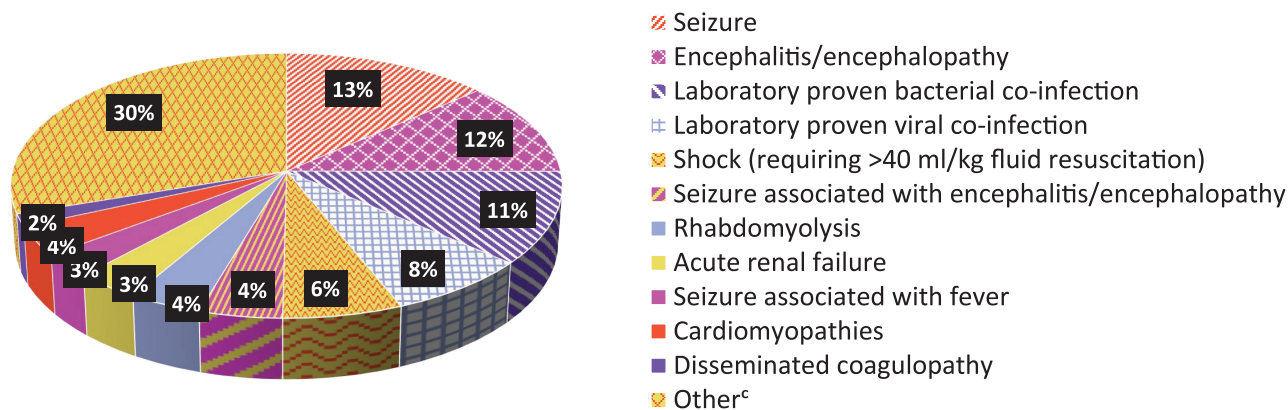
The APSU had previously conducted surveillance for CVS and neonatal varicella from 1995 to 1997,⁵¹ prior to the availability of varicella vaccinations in Australia and the introduction of fully-funded national vaccination for infants

Figure 4: Distribution and frequency of severe complications of influenza reported in 613 children aged < 15 years during 10 years of APSU surveillance (2008–2017)^a

Respiratory complications (n = 376)



Other (non-respiratory) complications (n = 727)



a Adapted from S Teutsch et al 2020.⁴²

b Other respiratory complications include: lung collapse, pneumothorax, apnoea, lung abscess, pleural effusion and fungal chest infection.

c 'Other' complications included: hyperglycemia, acute developmental regression, cardiac arrest, ventricular septal defects, urinary tract infection, thrombocytopenia, lactic and metabolic acidosis, subglottic stenosis, shock and multi-organ failure, pyomyositis, pericardial tamponade, perforation of eardrum, pancytopenia, pancreatitis, myositis, endocarditis, coagulopathy, marked hepatosplenomegaly, liver failure, Kawasaki disease, intracranial hemorrhage, electrolyte disturbances, hypoglycemia, hypertension, hemolytic uraemic syndrome, hepatitis, febrile neutropenia, flaccid paralysis, acute sickle chest syndrome, necrotising enterocolitis, transverse myelitis, purpura fulminans and Guillain-Barré syndrome.

in 2005.^{52,53} In that surveillance study, six cases of CVS and 44 cases of neonatal varicella infection were reported.⁵¹

In 2006, the APSU recommenced surveillance for CVS and neonatal varicella infection, both caused by varicella zoster virus (VZV), in order to assess the impact of varicella vaccination in Australia on the epidemiology of these two conditions.^{53, 54} In the 15 years since surveillance recommenced, a total of four confirmed cases of CVS and 31 cases of neonatal varicella infection have been reported to the APSU.

One notification of CVS in an Indigenous infant from New South Wales was reported to the APSU in 2020. The infant had laboratory-confirmed varicella infection and presented with encephalitis and was subsequently confirmed as a case. The most recent prior case of CVS was reported in 2017.⁴⁷

In 2020, no cases of neonatal varicella infection were reported in any Australian state or territory. This compares with three cases reported and confirmed in 2019.

In CVS, VZV is transmitted from infected mothers to their children during pregnancy. In neonatal varicella, VZV is transmitted four weeks before or after birth, either from an infected mother or via contact with another infected individual.⁵⁵ Congenital varicella can result in significant mortality and morbidity in infants, with abnormalities affecting the structure and function of multiple organ systems, including the CNS, eye, heart, gastrointestinal and genitourinary systems and skin. Neonatal varicella can cause a pox-like rash which may be papulovesicular, vesiculopustular or haemorrhagic, and fever.⁵⁶

Discussion and conclusions

In 2020, the APSU conducted surveillance of 14–16 rare childhood diseases, including ten communicable diseases or complications of communicable diseases. In March 2020, emergence of the SARS-CoV-2 novel coronavirus and

resulting global pandemic of COVID-19 led to implementation of significant emergency public health measures in Australia.⁵⁷ This resulted in a significant reduction in the transmission of SARS-CoV-2 and other communicable diseases in the community, including influenza.⁵⁸ The COVID-19 pandemic also caused significant disruption to the work routines of clinicians, including paediatricians, who were forced to adapt to changing, government-imposed safety restrictions. For example, in a 2020 survey, 572 Australian general practitioners reported an overall increase in workload due to the introduction of telehealth consultations and increased administration.⁵⁹ In spite of the prolonged impact of the pandemic on clinicians, there was a sustained participation by APSU contributors, with 91% of monthly report cards being returned. Although data collecting continued, there was a significant reduction in important APSU outputs, such as conference presentations, workshops, and education sessions for clinicians due to the travel restrictions and cancellations of face-to-face gatherings.

In 2020, the APSU/NERL and PAEDS systems identified sufficient AFP cases for Australia to meet the WHO target incidence rate of at least 1 non-polio AFP case per 100,000 children aged less than 15 years. This target rate has been consecutively achieved for the past 13 years and has enabled Australia to maintain its polio-free status.¹⁴ Review and classification of cases by the PEP in 2020 classified all AFP cases as non-polio AFP; the major diagnoses were GBS, transverse myelitis and ADEM, as in previous years.^{3,13} Internationally, there were global interruptions to polio vaccination of infants due to COVID-19 in 2020, including in countries with circulating wild-type poliovirus,^{60–62} placing Australia at greater risk of imported cases of polio and re-emphasising the importance of AFP surveillance and polio vaccination to ensure that Australia remains polio-free.

The lack of cases of severe complications of influenza reported to APSU in 2020 was consistent with significantly lower case numbers of influenza infection identified nationally.^{42,58} This

was likely the result of public health measures to prevent COVID-19 that prevailed throughout the Australian winter months, including closure of international borders, restricted movement of populations, physical distancing between individuals, encouragement of hand hygiene and the wearing of face masks,⁵⁸ as well as increased uptake of influenza vaccination.^{42,63} Ongoing surveillance of influenza by APSU and other systems will be required to determine whether the observed marked reduction of influenza persists in 2021 and subsequent seasons. Our 10-year study indicated that severe complications of influenza continue to occur in children, including those with no underlying medical condition, and that vaccination and antivirals are underutilised.⁴³

APSU surveillance of neonatal HSV infection is the world's longest continuous study of this condition. No demonstrated change in frequency has occurred over the 24-year study. In 2020, neonatal infection with both HSV-1 and HSV-2 serotypes was identified and resulted in SEM disease and CNS disease with localised, disseminated and asymptomatic presentations, indicating the variability of this rare disease. Death and severe sequelae persist in cases with neurological involvement, despite recommended increases in acyclovir dose and duration of therapy since 2001.³³ With no vaccine currently available for HSV, emphasis on preventative education and screening programs for expectant mothers and education for their treating clinicians is required. The large APSU surveillance dataset is enabling important trends to be examined over time, especially changes in treatment regimes, as clinical trials of antiviral treatment for this rare disease in infants do not reach the sample sizes required for meaningful statistical evaluation.⁶⁴

During 2020, APSU increased its engagement with cCMV and HIV study investigators to examine opportunities for enhancing reporting and improving case ascertainment. This resulted in more timely reporting of new cases of cCMV and HIV in 2020, and identification

and reporting of historic prevalent cases of both cCMV and HIV, allowing for adjustments of the estimates of incidence.

The incidence of cCMV infection has been stable since the 1990s and no vaccines are available to prevent mother-to-child transmission. Hygiene precautions are recommended to prevent infection, but not universal screening for CMV infection and use of antiviral therapy during pregnancy.²⁶ As this infection may result in death and disability in newborns, such as deafness, it is imperative that awareness of the risks of maternal and congenital infection are increased, both among expectant mothers and health care professionals.²⁶ The APSU cCMV surveillance study is the longest, continuously running study internationally and allows for the analysis of trends over long periods of time, and can be utilised to inform changes in policy, diagnostics, and antiviral treatment and potential vaccination strategies. Indeed, we have already shown that the use of antiviral therapy to treat infants with symptomatic infection has increased over time.²⁵

As the population of people living with HIV increases, due to the availability and use of antiretroviral treatment contributing to significantly improved life expectancy, more women living with HIV are having children. Although our APSU surveillance in 2020 found a high incidence of perinatal exposure to HIV, no cases of MTCT were identified at the time of reporting, and cases of MTCT have been very low in previous APSU reports.^{3,13} Current Australian guidelines recommend that pregnant women at high risk are offered antenatal HIV testing and, should they test HIV-positive, they be offered interventions known to be effective in reducing MTCT such as antiretroviral therapy during pregnancy, elective caesarean delivery and avoidance of breastfeeding.^{65,66} However, ongoing surveillance of perinatal exposure and MTCT is important, especially as most (77%) mothers of infants notified in 2020 were born outside Australia in countries where HIV infection is highly prevalent and where mothers may not receive adequate testing

and treatment. Children with paediatric HIV infection continue to be identified at low levels; however, importation of new cases from countries with high HIV prevalence is of ongoing concern.

The absence of congenital rubella cases for several consecutive years reflects the impact of vaccination in Australia.⁶⁷ In 2005, a nationally-funded varicella vaccination became available for young children, as well as a catch-up program for adolescents;⁵² however, a report to the APSU in 2020 of an Indigenous infant with confirmed congenital varicella syndrome raises questions about gaps in vaccination coverage, particularly in Indigenous populations.⁶⁸ Indeed, measles-mumps-rubella-varicella (MMRV) vaccination of young children in some Australian regions is lower than the national average, putting some children at risk.⁶⁸ Surveillance for rare vaccine-preventable infections thus remains important, as does recognition of the increased risks of vaccine-preventable congenital infections in children of Indigenous women in case of incomplete vaccination coverage.

Australia's national HPV vaccination program was implemented in 2007, initially for females aged 12 to 26 years, using a quadrivalent vaccine providing coverage for HPV types that may cause JoRRP, with a corresponding sharp decrease in rates of genital diseases associated with HPV 6 and 11 observed.^{69,70} The program has since been extended to include all children aged 12 to 13 years using a nonavalent HPV vaccine. The sustained decline in new cases of JoRRP identified by APSU surveillance reflects the high rates of HPV vaccination in women of childbearing age. Ongoing surveillance of JoRRP in Australia will be important, however, as there are potential gaps in vaccination in Australia of migrant and refugee women from countries without HPV vaccination programs.

The APSU has been a member of the International Network of Paediatric Surveillance Units (INOPSU) since its inception in 1998.⁷¹ The INOPSU network currently has 12 members that use similar surveillance methods

to APSU to collect data about rare childhood conditions.⁷² Surveillance for communicable diseases and their complications has been conducted by INOPSU members at varying times for: AFP (British, Canadian, Irish, New Zealand and Swiss units), congenital CMV (British, Canadian, New Zealand, Portuguese and Swiss units), CRS (British, Canadian, New Zealand, Netherlands and Swiss units), HIV infection and perinatal exposure to HIV (British, Netherlands and New Zealand units) and neonatal HSV (British, Canadian, German, New Zealand and Swiss units).⁷³ Surveillance of the same diseases by INOPSU units has enabled comparisons to be drawn, for example for AFP surveillance.⁷⁴

The APSU surveillance system continues to provide a reliable and effective means of collecting national prospective data on rare communicable diseases and their complications in children, reliant predominantly on monthly reports from paediatricians. Long-term surveillance of the conditions presented in this report enables assessment of trends in rates of infection and impacts of disease management and provides unique data to inform policy, education, vaccination and treatment strategies.

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Appendix A

Table A.1: APSU conditions under surveillance

Surveillance study – Case definition
<p>Acute flaccid paralysis (AFP)</p> <ul style="list-style-type: none">• Any child less than 15 years of age with acute flaccid paralysis in one or more limbs or acute onset of bulbar paralysis.• All cases reported through APSU, NERL and PAEDS are reviewed by the PEP and classified as: confirmed poliomyelitis; non-polio AFP, polio-compatible or non-AFP. The NERL determines whether there is an infectious cause of AFP including enteroviruses.• The PEP secretariat reports all Australian cases to the World Health Organization (WHO).
<p>Congenital cytomegalovirus (CMV) infection</p> <ul style="list-style-type: none">• Congenital CMV: Any child from whom CMV is isolated in the first three (3) weeks of life, from urine, blood, saliva, or any tissue taken at biopsy.• Suspected congenital CMV: any child up to 12 months of age, in whom CMV is isolated from urine, blood, saliva or any tissue taken at biopsy <i>and/or</i> a positive serum IgM is found <i>and</i> in whom clinical features exist that may be due to intrauterine CMV infection.• Clinical features associated with congenital CMV infection include: prematurity, low birth weight, sensorineural deafness, other neurological abnormalities (encephalitis, microcephaly, developmental delay), seizures, microphthalmia, chorioretinitis, cataracts), hepatitis, hepatosplenomegaly, thrombocytopenia, pneumonitis or myocarditis.
<p>Neonatal and young infant herpes simplex virus (HSV) infection</p> <ul style="list-style-type: none">• Any neonate or infant aged less than 3 months of age (regardless of gestation) seen in the last month with laboratory confirmation of HSV infection <i>and</i> with either clinical evidence of HSV infection <i>or</i> laboratory confirmation of maternal perinatal HSV infection in an asymptomatic infant.• Laboratory confirmation is by detection of HSV by PCR in a surface swab, respiratory specimen <i>and/or</i> sterile site (CSF or blood) (or by virus isolation), or by immunofluorescence.• Clinical evidence of neonatal HSV infection is one or more of: typical herpetic lesions of the skin, eye or mouth; evidence of disseminated infection (bleeding, bruising or coagulopathy, jaundice or elevated serum bilirubin, hepatosplenomegaly or elevated liver transaminases), pneumonitis (respiratory distress or chest radiograph) or encephalitis (lethargy, seizures, apnoea or abnormalities on neuroimaging or EEG).• Laboratory evidence of maternal perinatal HSV infection is provided by detection of HSV in maternal genital swab <i>and /or</i> mother seroconverted to HSV or IgM positive in pregnancy or early postnatal period.
<p>Paediatric human immunodeficiency virus (HIV) infection and perinatal exposure to HIV in Australia</p> <ul style="list-style-type: none">• Any child aged less than 16 years at diagnosis of HIV infection in Australia or any child born to a woman with diagnosed HIV infection. Children born to women with HIV infection and who are known to have been exposed to HIV perinatally, by <i>in utero</i> exposure or through breastfeeding, should be notified, even if they are subsequently confirmed as HIV antibody negative.
<p>Juvenile onset recurrent respiratory papillomatosis (JoRRP)</p> <ul style="list-style-type: none">• Any infant or child under the age of 15 years diagnosed with juvenile onset recurrent respiratory papillomatosis (JoRRP) confirmed by endoscopy of the larynx <i>and</i> by histology.

Surveillance study – Case definition

Severe complications of influenza in children < 15 years (May–September 2020)

- Any child aged less than 15 years with laboratory confirmed influenza admitted to hospital with at least one of the following complications:
- Pneumonia (confirmed radiologically and/or microbiology)
- Acute Respiratory Distress Syndrome (ARDS)
- Laboratory proven viral co-infection including COVID-19
- Laboratory proven bacterial co-infection; Bacteraemia; Septicaemia
- Encephalitis / encephalopathy
- Seizures (including simple febrile seizure, prolonged or focal seizure or status epilepticus)
- Transverse myelitis
- Polyneuritis / mononeuritis
- Guillain-Barré syndrome
- Reye Syndrome
- Myocarditis; Pericarditis; Cardiomyopathy
- Rhabdomyolysis
- Purpura fulminans
- Disseminated intravascular coagulopathy
- Shock (requiring >40 ml/kg fluid resuscitation)
- Acute renal failure
- Death, including death at presentation to hospital
- Requirement for supplementary oxygen, non-invasive ventilation, invasive ventilation or Extracorporeal Membrane Oxygenation (ECMO)

Congenital rubella syndrome (CRS)

Any child or adolescent up to 16 years of age who in the opinion of the notifying paediatrician has definite or suspected congenital rubella, with or without defects, based on history, clinical and laboratory findings.

Neonatal varicella infection

Any infant who has neonatal varicella based on history, clinical and/or laboratory findings in the first month of life without features of congenital varicella syndrome.

Features of neonatal varicella infection include pox-like rash which may be papulovesicular, vesiculopustular or haemorrhagic, and fever. Other systemic symptoms may be present. Complications of neonatal varicella include bacterial superinfection, neurological and haematological problems and general visceral involvement.

The diagnosis of neonatal varicella can be made when an infant in the first month of life presents with clinical features of varicella infection. There may be a history of maternal varicella infection in the last 1–4 weeks of pregnancy or contact with a varicella infected person after birth.

The diagnosis can be confirmed by laboratory tests to detect:

- Viral antigen/viral isolate from scrapings of the skin lesions or viral DNA from lesion fluid.
- Varicella specific IgM in a serum sample from the infant (or from the contact).

Congenital varicella

Any stillbirth, newborn infant, or child up to the age of 2 years who, has definite or suspected congenital varicella infection, with or without defects and meets at least one of the following criteria:

- Cicatricial skin lesions in a dermatomal distribution and/or pox-like skin scars and/ or limb hypoplasia.
- Development of herpes zoster in the first year of life.
- Spontaneous abortion, termination, stillbirth or early death following varicella infection during pregnancy.

Confirm varicella infection by one or more of the following:

- Detection of varicella-specific IgM antibodies in cord blood or in serum specimen taken in the first 3 months of life (only 25% of cases are positive).
- Persistence of varicella specific IgG antibody in a child aged beyond 6 months of age.
- Identification of varicella virus in skin lesions or autopsy tissue.
- History of maternal varicella during pregnancy or maternal contact with varicella in pregnancy in the mother of an infant with congenital abnormalities.

The following clinical signs may also be present in cases of congenital varicella syndrome:

- Microcephaly, hydrocephalus, cerebellar hypoplasia, motor or sensory deficits, sphincter dysfunction and peripheral nervous system defects.
- Microphthalmia, cataracts, Horner's syndrome, chorioretinitis, nystagmus, retinal scars, optic atrophy.
- Gastrointestinal abnormalities including colonic atresia, hepatitis, liver failure.
- Genito-urinary abnormalities.
- Cardiovascular abnormalities.
- Intrauterine growth retardation.