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Prospective characterisation of SARS-CoV-2 infections among children presenting to tertiary paediatric hospitals across Australia in 2020: a national cohort study

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ABSTRACT

Objective To present Australia-wide data on paediatric COVID-19 and multisystem inflammatory syndromes to inform health service provision and vaccination prioritisation.

Design Prospective, multicentre cohort study.

Setting Eight tertiary paediatric hospitals across six Australian states and territories in an established research surveillance network—Paediatric Active Enhanced Disease (PAEDS).

Participants All children aged <19 years with SARS-CoV-2 infection including COVID-19, Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) and Kawasaki-like disease TS infection (KD-TS) treated at a PAEDS site from 24 March 2020 to 31 December 2020.

Intervention Laboratory-confirmed SARS-CoV-2 infection.

Main outcome Incidence of severe disease among children with COVID-19, PIMS-TS and KD-TS. We also compared KD epidemiology before and during the COVID-19 pandemic.

Results Among 386 children with SARS-CoV-2 infection, 381 (98.7%) had COVID-19 (median 6.3 years (IQR 2.1–12.8),53.3% male) and 5 (1.3%) had multisystem inflammatory syndromes (PIMS-TS, n=4; KD-TS, n=1) (median 7.9 years (IQR 7.8–9.8)). Most children with COVID-19 (n=278; 73%) were Australian-born from jurisdictions with highest community transmission. Comorbidities were present in 72 (18.9%); cardiac and respiratory comorbidities were most common (n=32/72;44%). 37 (9.7%) children with COVID-19 were hospitalised, and two (0.5%) required intensive care. Postinfective inflammatory syndromes (PIMS-TS/KD-TS) were uncommon (n=5; 1.3%), all were hospitalised and three (3/5; 60%) required intensive care management. All children recovered and there were no deaths. KD incidence remained stable during the pandemic compared with prepandemic.

Conclusions Most children with COVID-19 had mild disease. Severe disease was less frequent than reported in high prevalence settings. Preventative strategies, such as vaccination, including children and adolescents, could reduce both the acute and postinfective manifestations of the disease.

Strengths and limitations of this study

- ► A major strength of this study is the inclusion of all known SARS-CoV-2 positive children presenting to tertiary paediatric hospitals across Australia in 2020.
- ► The vast majority of SARS-CoV-2 infections in 2020 in Australia were from a single ancestral lineage, as new SARS-CoV2 variants emerge, this data will provide a basis for comparison to future years.
- ► Overall low case numbers in Australia in 2020 limited the evaluation of risk factors for severe disease in the paediatric population.
- ► The population-level high infection ascertainment in Australia supports a highly accurate denominator for use in calculating incidence estimates of paediatric disease and its outcomes.

INTRODUCTION

To date, SARS-CoV-2, responsible for the global pandemic of COVID-19, has resulted in over 220 million confirmed cases and over 4.5 million deaths globally.[1] The Americas, Europe and South-East Asia have been the most severely affected regions, with the USA reporting the highest incidence of any country (~12 078 confirmed cases per 100 000 population).[1] The lack of widespread testing among children in many settings has limited

the accuracy of incidence estimates in the paediatric population.

In comparison, Australia had a very low prevalence of COVID-19 in 2020 (~118 cases per 100 000 population) and among the highest SARS-CoV-2 testing rates in the world (~599 tests per case; 0.17% positive).[1] Australia's water-locked geography and extensive public health infrastructure enabled effective suppression of community-based transmission of SARS-CoV-2 in all states and territories in 2020. Early closure of international borders, widespread accessibility to SARS-CoV-2 testing, rapid case identification and agile contact tracing mechanisms helped to mitigate the spread of the virus in the first year of the pandemic.[2] Wastewater surveillance for SARS-CoV-2 has been used as an early-warning indicator of community viral transmission.[3] In 2020, a total of 3920 cases in children aged 0–19 years were notified to the Australian Government Department of Health.[4] Australia has a distributed testing model whereby the majority of testing is performing in designated community COVID-19 testing locations. Hence, a subset of positive paediatric cases are diagnosed and/or managed in tertiary paediatric centres and these were captured in this study.

The PAEDS network (Paediatric Active Enhanced Disease Surveillance)[5] is a hospital-based active sentinel surveillance network that, in collaboration with Influenza Complications Alert Network (FluCAN),[5 6] collects observational data on serious diseases of public health importance. At the onset of the COVID-19 pandemic, the PAEDS and FluCAN networks rapidly incorporated COVID-19 and Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS, also known as Multisystem Inflammatory Syndrome in Children)[7 8] as previously defined (box 1),[9] into their surveillance programme. PAEDS has also undertaken national surveillance for Kawasaki disease (KD) since 2019, allowing comparison of KD epidemiology prior to and during the COVID-19 pandemic.

We aimed to describe Australia-wide data on the clinical, demographic and laboratory characteristics and outcomes of children with SARS-CoV-2 infection presenting to paediatric hospitals throughout 2020, the first year of the pandemic. We also present surveillance data on KD prior to and during the COVID-19 pandemic to investigate whether these may indicate unascertained PIMS-TS cases.

Box 1 Case definition of Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-COV-2 (PIMS-TS)

Clinical

Children and adolescents (up to 18 years of age) with fever ≥3 days.
and two of the following:

- Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
- Age-specific hypotension or 'shock' within first 24 hours of presentation.
- Features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities [including echocardiogram findings or elevated Troponin/N-terminal pro b-type natriuretic peptide (NT-pro-BNP)].
- Evidence of coagulopathy [by prothrombin time (PT), partial thromboplastin time(PTT), elevated D-dimers].
- Acute gastrointestinal problems (diarrhoea, vomiting or abdominal pain).

And elevated markers of inflammation such as erythrocyte sedimentation rate (ESR), C reactive protein (CRP) or procalcitonin.
And exclusion of other infectious causes of inflammation, including bacterial sepsis, staphylococcal or streptococcal toxic shock syndromes.

Laboratory

And evidence of SARS-CoV-2 infection (positive reverse-transcriptase-PCR), or confirmed contact with a person with SARS-CoV-2 infection (public health defined), or confirmed positive SARS-CoV-2 serology (noting testing may be delayed, particularly serology. If all other criteria are met, collect data pending results).
Source: Paediatric Active Enhanced Disease Surveillance: PIMS-TS-https://paeds.org.au/web/our-work/surveillance-and-research.[9 13]

METHODS

Study population, setting and data collection

Children aged 0–19 years were prospectively identified across eight Australian tertiary referral children's hospitals from six (of eight) Australian states and territories by the PAEDS network between 27 March 2020 and 31 December 2020. Retrospective review of hospital laboratory notifications occurred for the period 1 January to 26 March[10–12] and showed the first positive case at our institutions was detected on 24 March. Testing practices were guided by jurisdictional public health directives. Nasopharyngeal/oropharyngeal SARS-CoV-2 reverse-transcriptase PCR (RT-PCR) was undertaken in children with viral symptoms (eg, cough, fever, sore throat, runny nose, headache, loss of smell/taste) and/or any child (asymptomatic or symptomatic) with known contact with a SARS-CoV-2-infected individual/s.[2] This included inpatients, outpatients and children presenting to emergency departments in any PAEDS hospital. A positive SARS-CoV-2 test on RT-PCR was considered confirmation of infection.

A subset of children underwent SARS-CoV2 serology testing as an alternative means of confirming infection. The main indication for serology was as part of the diagnostic workup for PIMS-TS.[7 8] A diagnosis of PIMS-TS was based on our previously published case definition (box 1)[13] and that of KD (KD-TS) was made in PIMS-TS patients who had a clinical pattern consistent with KD (met classical criteria for KD) and also had evidence of SARS-CoV-2 infection or exposure (positive PCR and/or serology). A diagnosis of KD not associated with SARS-CoV-2 (as opposed to KD-TS) was made in those that fulfilled clinical criteria for this condition and had no laboratory evidence of recent or past SARS-CoV-2 infection and no known epidemiological links.

Researchers were notified by the clinical laboratory of all positive patients. Any child with suspected or

confirmed PIMS-TS or KD-TS was notified to a PAEDS investigator (if RT-PCR or serology positive) and/or via the child's treating clinician. Incidence of PIMS-TS in relation to SARS-CoV-2 positive cases in children <19 years was calculated. Nationwide data were used as the denominator for PIMS-TS incidence estimates. Severe (or critical) disease was defined by need for respiratory support (high-flow nasal prong oxygen therapy, non-invasive or invasive ventilation or extracorporeal membrane oxygenation (ECMO)) and/or inotropic support.[14] Admission to intensive care unit was based on individual clinician discretion with consideration of patient age and comorbidities, potential to deteriorate or worsen, infection control (more controlled environment in intensive care compared with the medical ward) and bed availability.

Clinical data were obtained from medical records and direct interview of parents using a standardised clinical data collection form under a waiver of consent (The Royal Children's Hospital, Melbourne and Sydney Children's Hospitals Network Human Research and Ethics Committee Approvals; reference HREC 63103 and HREC/18/SCHN/72, respectively). Guidelines for high-quality retrospective data collection were followed.[15] Data were entered into a Research Electronic Data Capture online database V.10.7.1 (hosted by the respective research institute at each site). PAEDS national surveillance of KD, commencing January 2019 to December 2020, was included for comparison. KD diagnosis was based on published criteria.[16]

Patient and public involvement

Due to the rapidly evolving nature of the pandemic, patients were not involved in the design of this study.

Statistical analysis

For this descriptive analysis, continuous variables (eg, age, number of symptoms and length of stay) were described using median and IQR. Categorical variables were summarised by number (n) and percentage (%). Associations between symptoms were reported using tetrachoric correlation coefficient of the two binary variables. Stata V.16 (StataCorp) was used for data analysis.

RESULTS

As of 31 December 2020, 124 304 SARS-CoV-2 tests were performed across seven of eight PAED sites (denominator testing numbers from one PAEDS sites unavailable), of which 384 children tested positive, the majority (n=381; 99%) confirmed on RT-PCR of oropharyngeal/nasopharyngeal samples and three (0.8%) confirmed on SARS-CoV-2 serology alone (PCR negative). An additional two children with probable PIMS-TS with strong epidemiological evidence (close contact confirmed case in a household or school OR residence in a location with high-level community transmission) had negative PCR and serology. The single child with KD-TS had both recent positive PCR and serology. Most children were diagnosed with COVID-19 (381; 98.7%), four had PIMS-TS and one had KD-TS. The median age across the entire cohort was 6.5 years (IQR 2.1–12.8) and 207 (53.6%) were male. The majority of children had known contact with a positive case (n=270/381; 70.9%), usually one or more household members (n=195/270; 72.2%). Almost two-thirds of children with COVID-19 (n=244/381; 64%) and all with PIMS-TS (n=5/5) were symptomatic. Asymptomatic children were identified as part of contact tracing in the context of household positive contacts or school/child-care outbreaks. Baseline characteristics groups are shown in table 1. To maintain confidentiality, demographics from the single case with KD-TS have been omitted.

Almost one in five children (n=72/381, 18.9%) with COVID-19 had at least one pre-existing comorbidity. The most common comorbidities were respiratory (n=25/72, 34.7%, of which 21/25, 84% had asthma), cardiac (n=9/72, 12.5%), neurological (n=8/72, 11.1%) and ear, nose and throat condition (n=8/72, 11.1%) (see figure 1). Almost one-third, (n=22/72, 30.6%) had more than one comorbidity and cardiac and/or respiratory comorbidities were most common (n=32/72; 44.4%). A range of cardiac comorbidities were reported, including complex congenital heart disease (5/9, 55.5%), isolated septal defects (2, 22%) and one each of prolonged QTc interval and hypertension. Among children admitted to hospital with COVID-19 (in-hospital and hospital-at-home), more than a quarter (18/65; 27.7%) reported one or more comorbidity. The most common comorbidity observed were cardiorespiratory conditions reported in 50% (n=9/18) of those with comorbidities, followed by neurological and immune-deficiency (n=4, 22.2%; n=3, 16.7%, respectively).

The median duration of symptoms prior to presentation was 2 days (IQR 0–3). Most children with COVID-19 had symptoms (244/381; 64%) at the time of testing, with most having >1 symptom (81.7%) and over one-third (84/231, 36.4%) reporting four or more symptoms. Coryza, cough and fever were the most common symptoms (median age of children ranged from 3.2 to 3.7 years) and often co-occurred (figure 2), followed by sore throat, fatigue/malaise and headache (table 2). Sore throat and headache were reported in older children (21/223; 9% of all children, median age with both symptoms, 12.3 years). Gastrointestinal symptoms (nausea/vomiting or diarrhoea) were common in younger children and reported in 45 (19%) children, with a median age of 5.6 years (IQR 1.0–9.8) (table 2). The median age of asymptomatic children was 7 years (IQR 2.8–12.1), compared with 5.7 years (IQR 1.5–13.0) for symptomatic children. While most children had mild disease, 18% (n=70/386) were admitted to hospital (table 3). Children with PIMS-TS and KD-TS had longer lengths of stay compared with those with COVID-19 (table 3). Three of the five children with PIMS-TS or KD-TS were admitted to the intensive care unit compared with two with COVID-19 (n=2/65; 3.1%). Invasive ventilation was administered in one child with COVID-19 and ECMO was

Table 1 Characteristics of 385 children with SARS-CoV2 related disease managed at eight Australian paediatric hospitals

	COVID-19	PIMS-TS
	N=381	N=4
Characteristics of children	n (%)	n
Age (in years), median (IQR)	6.3 (2.1–12.8)	8.9 (7.9–11.0)
Sex		
Male	203 (53.3)	3
Female	178 (46.7)	1
Country of birth		
Australia	278 (73.0)	3
Other	103 (27.0)	1
Aboriginal or Torres Strait Islander (TSI)		
Neither	371 (97.4)	4
Aboriginal	3 (0.8)	0
Both Aboriginal and TSI	1 (0.3)	0
Unknown	6 (1.6)	0
Health service		
The Royal Children's Hospital, Melbourne, VIC	178 (46.7)	2
Monash Health, Melbourne, VIC	95 (24.9)	1
Children's Hosp. Westmead, Sydney, NSW	66 (17.3)	1
Sydney Children's Hospital, Sydney, NSW	20 (5.2)	0
Queensland Children's Hospital, Brisbane, QLD	12 (3.1)	0
Women's and Children's Hospital, Adelaide, SA	8 (2.1)	0
Perth Children's Hospital, Perth, WA	1 (0.3)	0
Royal Darwin Hospital, Darwin, NT	1 (0.3)	0
Admission	65 (17.1)	4
Hospital-at-home programme	28 (43.1)	N/A
In-hospital care	37 (56.9)	4
Has the child had contact with a confirmed case?		
No	82 (21.5)	2
Yes	270 (70.9)	2
Unknown	29 (7.6)	0
Was the confirmed case a household contact?		
No	47 (17.4)	1
Yes	195 (72.2)	1
Unknown	28 (10.4)	0
If yes, how many household contacts (excluding child) in total were positive? median (IQR)	3.0 (2.0–4.0)	1.0*

Note: a single case of KD-TS was observed, omitted from table to maintain confidentiality.
*Data available from one child.
NSW, New South Wales; NT, Northern Territory; PIMS-TS, Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 infection; QLD, Queensland; SA, South Australia; VIC, Victoria; WA, Western Australia.

required in one child with PIMS-TS. Empiric antibiotics were administered to eight (12%) hospitalised children with COVID-19 and all with PIMS-TS and KD-TS. Antiviral (remdesivir) was given to two with COVID-19 (3%) and one child with PIMS-TS (25%). Systemic corticosteroids were administered to five children with COVID-19 (7.7%) and all with PIMS-TS and KD-TS received both corticosteroids and intravenous immunoglobulin. Three with PIMS-TS and the one child with KD-TS received thromboprophylaxis with low molecular weight heparin or enoxaparin. There were no deaths.

Using nationwide infection data as a denominator[4 17] (n=3920, SARS-CoV-2 positive cases in children <19 years notified in 2020[4]), the incidence of confirmed PIMS-TS/

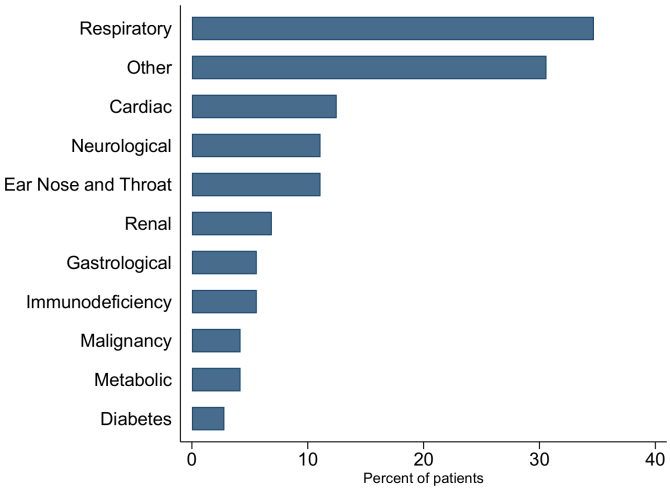

Figure 1 Comorbidities among children (n=72 of 381) with COVID-19.

KD-TS was 3 per 3920 (0.08%) confirmed cases among SARS-CoV-2 infected children (77 per 100 000 infections). KD surveillance prior to and during the COVID-19 pandemic showed no increase in cases in 2020 compared with 2019 with 3-month moving average remaining stable throughout 2020 despite a steep rise in COVID-19 cases in July/August (figure 3).

DISCUSSION

This is the most comprehensive report of SARS-CoV-2 infections in Australian children. We provide a systematic overview of the clinical characteristics and outcomes of almost 400 children presenting to tertiary paediatric hospitals across Australia during the first year of the COVID-19 pandemic. Our findings show that the great

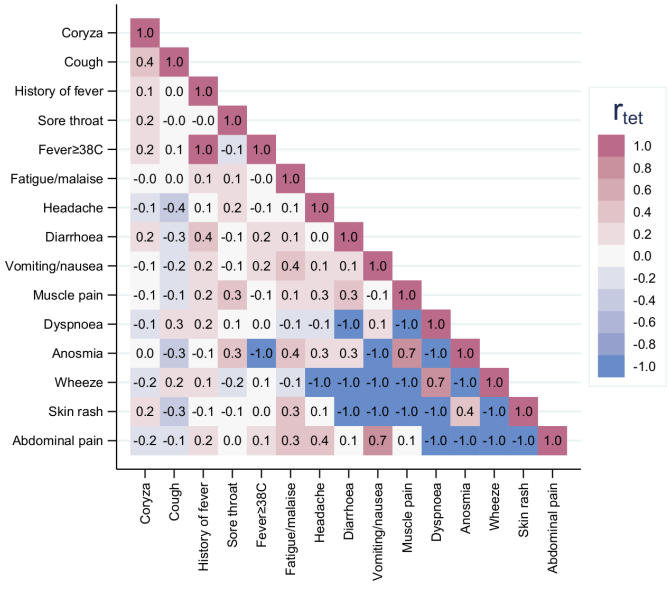

Figure 2 Heatmap showing tetrachoric correlation coefficient between two symptoms (n=187) demonstrating clustering of symptoms such as anosmia and muscle pain among the symptoms with minimum 10 patients.

majority of Australian children with COVID-19 had mild disease and approximately one-third were asymptomatic. Furthermore, rates of postinfective multisystem inflammatory syndromes among SARS-CoV-2 positive Australian children were extremely low (77 per 100 000 infections), comparable with other low incidence settings.

Over one-third of our cohort had asymptomatic infection (137/381; 36%) which is substantially higher than the 5%–21% reported from China and Italy.[18–20] Furthermore, hospitalisation rates were lower in our cohort of SARS-CoV-2 positive children compared with higher-prevalence settings. Fewer than one in 10 (9.7%) infected children in our cohort required in-hospital care and two (0.5%) needed intensive care management (one requiring mechanical ventilation). There were no deaths in our cohort. This is in contrast to a large multicentre European study, where 62% of 582 SARS-CoV-2 positive children were hospitalised and 8% required intensive care management, with four deaths (case fatality rate 0.69%).[21] It is likely that high per population testing rates in Australia and resultant high case ascertainment has enabled more accurate denominator estimates, compared with high incidence countries, which may partly account for varying hospitalisation rates. Criteria for hospitalisation may also differ between countries. Furthermore, Australia performs pre-emptive testing of all close contacts of cases, irrelevant of symptom status, further increasing ascertainment rates.[22]

Consistent with other studies from low-incidence settings, the median age of children in our cohort was 6 years. Lu *et al* (n=171)[20] and Dong *et al* (n=731)[19] reported similar median ages of 6.7 and 7 years, respectively, from China. In contrast, a large Centers for Disease Control and Prevention report from the USA on 2572 children reported a median age of 11 years.[23] This may reflect lower testing rates among younger children in high prevalence settings, as younger children have high rates of mild or asymptomatic infection, however this is unclear. Most children in our cohort (>70%) had known contact with a positive case, usually one or both parent/s in the household. This concurs with studies from Italy, China and the US reporting infection occurring in the context of a family cluster in 45%–91% of children.[18 20 23]

Fever, cough and coryza were the the most common presenting symptoms, consistent with other paediatric studies.[18 19] Anosmia was reported in 5%, an uncommon symptom compared with adults in whom it is reported in 50% of cases.[24] However, this may reflect the limited ability of young children to describe their symptoms. Symptom duration prior to presentation was short (median 2 days) most likely reflecting adherence to directives to have SARS-CoV-2 testing at the onset of viral symptoms, rather than healthcare-seeking behaviour in response to worsening illness.

Comorbidities were common within our cohort with almost one in five (18.9%) with COVID-19 reporting one or more comorbidity. Respiratory (mainly asthma) and cardiac conditions were most frequent. This may

Table 2 Clinical manifestations in 244 children with COVID-19

Symptoms	N*	n (%)	Median age (IQR)
Coryza (runny nose, rhinorrhoea)	229	137 (59.8)	3.7 (1.2–10.9)
Cough	231	127 (55.0)	3.5 (1.1–12.5)
History of any fever	229	93 (40.6)	3.2 (1.0–8.6)
Sore throat	221	69 (31.1)	10.8 (4.0–15.2)
Fever ≥38°C	202	50 (24.8)	1.6 (0.9–5.1)
Fatigue/malaise	226	52 (22.9)	5.1 (1.2–13.1)
Headache	221	44 (19.9)	10.6 (6.5–15.3)
Diarrhoea	229	24 (10.5)	5.1 (1–8.5)
Vomiting/nausea	230	24 (10.5)	4.5 (1.4–9.6)
Muscle pain (myalgia)	220	18 (8.2)	10.4 (5.6–15.4)
Dyspnoea	227	15 (6.6)	11.5 (0.4–15.2)
Anosmia	219	11 (5.0)	15.3 (13.3–15.9)
Wheeze	228	10 (4.4)	2.3 (0.4–12.2)
Skin rash	229	10 (4.4)	0.8 (0.4–9.3)
Abdominal pain	221	10 (4.5)	6.8 (4.0–8.8)
Sneezing	230	8 (3.5)	2.0 (1.3–8.5)
Others	230	8 (3.5)	4.9 (2.2–7.4)
Hypogeusia	219	7 (3.2)	14.7 (10.5–16.3)
Lower chest wall indrawing	227	5 (2.2)	0.4 (0.4–2.2)
Ear pain	221	3 (1.4)	6.1 (2.4–6.3)
Seizures	229	3 (1.3)	8.6 (6–15.6)
Lymphadenopathy	224	3 (1.3)	4.0 (3.2–10.0)
Chest pain	221	2 (0.9)	12.9 (9.3–16.5)
Joint pain (arthralgia)	219	2 (0.9)	15.3 (12.8–17.9)
Altered consciousness/confusion	228	2 (0.9)	0.2 (0–0.4)
Skin ulcers	228	2 (0.9)	8.0 (0.3–15.8)
Conjunctivitis	228	1 (0.4)	12.2
No of symptoms or signs			
1	231	42 (18.2)	7.6 (3.1–12.5)
2	231	57 (24.7)	5 (1.2–13.0)
3	231	48 (20.8)	4.7 (1.4–12.0)
4+	231	84 (36.4)	3.1 (1.1–12.2)
Duration of symptoms or signs (in days), median (IQR)	207	2.0 (0.0–3.0)	

*Number with observed data (remainder as missing).

simply reflect a high background rate of comorbidities in children presenting to tertiary hospitals. Götzinger *et al* reported that children with pre-existing medical conditions were over threefold more likely to require intensive care unit admission,[21] Our group has shown that cardiorespiratory comorbidities are similar between SARS-CoV-2 positive and SARS-CoV-2 negative children, however, a disproportionately high number of hospitalisations occurred in children with cardiac comorbidities.[25] The low number of severe cases in our cohort precluded evaluation of the relationship between comorbidities and disease severity.

The proportion of PIMS-TS or KD-TS among hospitalised children (5/42; 11.9%) was lower in our cohort compared with US and German studies, which have reported PIMS-TS in 25%–27% of hospitalised children with SARS-CoV-2 infection.[26 27] This may reflect higher rates of PIMS-TS and KD-TS in these settings or more plausibly, Australian hospitals may have been able to exercise lower thresholds for hospitalisation of children compared with Europe and the USA where caseloads were much higher. Similar to US data, the proportion of those with PIMS-TS requiring intensive care in our study was higher than in those with acute COVID-19.[28]

Table 3 Characteristics and outcomes of children hospitalised (includes both in-hospital and hospital-at-home) with COVID-19, PIMS-TS and KD-TS

	COVID-19 N=65	PIMS-TS N=4	KD-TS N=1
Hospitalised	n (%)	n	n
Age at presentation(years, median (IQR))	4.0 (1.1–11.5)	9.8 (7.9–10.8)	1.0
Length of stay (in days), median (IQR)	3.0 (1.0–8.0)	11.0 (10.0–19.0)	6.0
Admitted to intensive care unit	2 (3.1%)	2	1
Respiratory support			
None	62 (95.4%)	3	1
Low-flow oxygen only	2 (3.1%)	0	0
High flow nasal oxygen therapy	0	0	0
Non-invasive ventilation	0	0	0
Invasive mechanical ventilation	1 (1.5%)	1	0
Inotropic support	1 (1.5%)	2	0
Extracorporeal (ECMO) support	0	1*	0
Discharge status (alive)	65 (100.0%)	4	1

*also received invasive mechanical ventilation
ECMO, extracorporeal membrane oxygenation; KD, Kawasaki disease; PIMS-TS, Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 infection.

In total, five cases of multisystem inflammatory complications were identified over the study period. Three were confirmed and two were probable cases on the basis of epidemiological links with positive cases. In Australia, most (if not all) cases of PIMS-TS and KD-TS are managed in PAEDS centres (PAEDS sites include all major tertiary paediatric hospitals across Australia). This is in line with current Australian guidelines recommending early consultation and transfer of suspected cases to tertiary paediatric centres.[29] The low incidence of confirmed cases among SARS-CoV-2 infected children (0.08%) is comparable to a recent report from South Korea, another low incidence country, where 3 PIMS-TS cases were identified among 4107 SARS-CoV-2 infected children (0.07%).[30] Interestingly, we observed relative stability in the number of KD cases during 2020 compared with the year prior to the pandemic. This is consistent with a study from South Korea reporting no increase in KD-related hospitalisations in 2020 compared with the preceding 4-year period[31] and a US study showing similar findings.[32] Epidemiological and laboratory data from higher incidence settings should increase understanding of the overlap and differentiation between PIMS-TS and KD, which are considered related but distinct syndromes.[33]

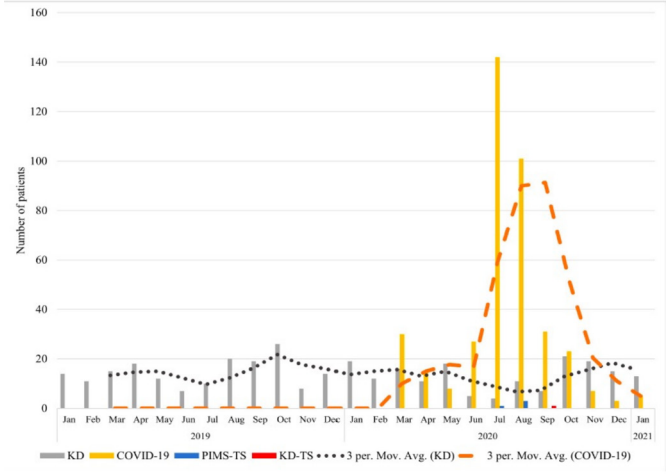

Figure 3 Epidemiology of Kawasaki disease (KD) prior to and during the COVID-19 pandemic with absolute numbers of COVID-19 (orange bars), (KD, grey bars), PIMS-TS (blue bars) and KD-TS (red bars) cases and 3 months moving average illustrating KD cases remained stable during 2020 in comparison to 2019. PIMS-TS, Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 infection.

There are a number of strengths to our study. The national aggregation of cases in the context of a low-prevalence of SARS-CoV-2 infection in Australia, with very high testing rates and case ascertainment allowed accurate infection denominator estimates. Since Australia has achieved complete suppression of community-based transmission during multiple periods in the pandemic due to aggressive public health measures, the incidence estimates for severe outcomes from this study have a high level of confidence. Our findings could help predict infection rates relative to hospitalisation and severe disease in other populations with lower testing rates. Second, our comprehensive national surveillance with inclusion of all laboratory-confirmed SARS-CoV-2 positive children from every Australian tertiary-level children's hospital, provides a comprehensive overview of this disease in Australian children. Importantly, these data reflect infection predominantly with lineage D.2, which was responsible for over 98% of cases during Melbourne, Victoria's second wave

in 2020.[34] The PAEDS network is continuing surveillance with comprehensive data on a large delta variant point-source outbreak in Eastern Australia in 2021. This will afford opportunities to compare the severity of these two variants over time in children.

There are a number of limitations of this descriptive study. Due to the very low numbers of children with severe COVID-19, our study was not able to evaluate risk factors for severe disease. Second, as we included participants presenting to tertiary paediatric hospitals, we acknowledge potential selection bias that may be present, with higher-risk children (ie, those with chronic medical conditions) likely to preferentially present to their treating hospitals for testing. This may have resulted in an overestimation of the severity of COVID-19 cases in general when we used admission as a measure of severity. Third, viral genomic data from participants was not included and it is plausible that variants with differing transmissibility and pathogenicity may impact these findings. Lastly, some but not all KD cases had serological testing to exclude past SARS-CoV-2 infection. However, a paediatric specific national serosurvey performed by the PAEDS network (unpublished, Dr Archana Koirala personal correspondence) in late 2020 confirms extremely low seroprevalence, reducing the likelihood of misclassification bias.

In summary, in our cohort of children with SARS-CoV-2 infection from all tertiary paediatric hospitals across Australia, the majority had mild or asymptomatic disease and need for intensive care management was much less common than in high-prevalence regions. Postinfective multisystem inflammatory syndromes, while rare, were associated with high morbidity and intensive care unit management. When evaluating the benefits of vaccinating children, the potential direct benefits of protecting against severe COVID-19 as well as postinfective inflammatory conditions need to be considered. A recent recommendation from the Australian Technical Advisory Group on Immunisation, has informed a decision by the Australian Government to introduce universal vaccination for all individuals from 12 years of age and older from September 2021.

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