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Australian Vasculitis Working Group and Paediatric Active Enhanced Disease Surveillance (PAEDS) network

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Lower risk of multi-system inflammatory syndrome in children (MIS-C) with the omicron variant

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Multi-system inflammatory syndrome in children (MIS-C), also known as pediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 (PIMS-TS), is an infrequent but severe post-infectious complication of COVID-19.[1] The Paediatric Active Enhanced Disease Surveillance (PAEDS) network (www.paeds.org.au)[2] initiated sentinel surveillance for MIS-C in May 2020. PAEDS used a case definition for MIS-C modified from the WHO definition (supplementary methods). PAEDS concurrently undertook surveillance for hospitalized COVID-19 and Kawasaki disease.[3]

SARS-CoV-2 infections were classified as occurring during three periods according to the dominant SARS-CoV-2 variant circulating[3,4]: Pre-Delta/ancestral strains from March 2020 to May 2021, Delta variant of concern (VoC; B.1.617.2) from June to November 2021 and Omicron (B.1.1.529) variants December 2021 to April 2022. The variant at the time of SARS-CoV-2 infection for each MIS-C case was presumed to be the dominant variant circulating 28 days before symptom onset, assuming an average 4-week lag between infection and MIS-C onset.[1,2] A SARS-CoV-2 infection-related incidence rate of MIS-C was calculated in those states with publicly available infection notification data in persons aged 0-<19 years.

PAEDS identified 107 cases of MIS-C from 1 May 2020 to 30 April 2022. Of these, 5 (5%) were associated with the pre-Delta period, 30 (28%) with the Delta VoC wave and 72 (67%) with Omicron waves. MIS-C was most frequent in children aged 5-<12years (n = 61, 57%). ICU admission was required in 23 cases (22%); there were no deaths. MIS-C cases peaked 4–8 weeks after peaks in COVID-19 admitted cases in children (Supplementary Figure). During the pre-Delta period, the MIS-C rate was 13 cases per 10,000 (95% confidence interval [CI]: 4–29) SARS-CoV-2 notified infections in those aged 0–19 years (Table 1). This rate reduced to 5 per 10,000 (95% CI: 4–7) during the Delta period and decreased further to 0.8 per 10,000 (95% CI: 0–1) during the Omicron period.

We provide evidence for a reduction in the infection-related frequency of MIS-C in children across the COVID-19 pandemic in Australia, particularly associated with Omicron variants. These data support a similar finding in the United Kingdom, Israel and Denmark where significantly lower rates of MIS-C relative to SARS-CoV-2 infections have occurred in association with Omicron VoC.[5–7]

Prior infection-related immunity to SARS-CoV-2 is unlikely to have contributed substantially to the observed reduction in MIS-C rates. Our PAEDS serosurvey showed a very low population rate of infection in Australian children prior to the Delta wave,[8] and total Delta wave notifications occurred in only 2% of the child population. The Australian COVID vaccination program for 5–11 year olds began on 10 January 2022; only 36.7% of children in this age group had received two doses by 30th April and children aged <5 years were ineligible.[9] A minority of MIS-C cases (n=20; 19%) were aged >12 years

Abbreviations: PAEDS, Paediatric Active Enhanced Disease Surveillance network; MIS-C, Multi-system Inflammatory Syndrome in Children

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[1] A complete list of group members appears in the Acknowledgments.

Jurisdiction	Pre-Delta			Delta			Omicron		
	MIS-C cases (n)	COVID-19 cases (N)	Incidence rate per 10,000 notifications (95% CI)[a,b]	MIS-C cases[a] (n)	COVID-19 cases (N)	Incidence rate per 10,000 notifications (95% CI)[a,b]	MIS-C cases (n)	COVID-19 cases (N)	Incidence rate per 10,000 notifcations (95% CI)[a,b]
NSW	2	560	**36 (4–128)**	10	25,072	**4 (2–7)**	27	471,671	**0.6 (0–1)**
Victoria	3	3306	**9 (2–26)**	20	33,562	**6 (4–9)**	28	142,892	**2 (1–3)**
QLD	0	108	**0**	0	168	**0**	5	112,175	**0.4 (0–1)**
Overall	5	3974	**13 (4–29)**	30	58,802	**5 (4–7)**	60	726,738	**0.8 (0–1)**

***Table 1*: Infection-related incidence of MIS-C among children aged 0–<19 infected with SARS-CoV-2 by dominant variant and jurisdictional notification rates.**

[a] Notifications used as denominator data; in NSW these are aged are 0 to <19 years, PCR and rapid antigen (RAT) tests); in Victoria are 0 to and including 19 years, PCR tests only; and in QLD are 0 to and including 19 years, PCR and RAT tests.

[b] Confidence intervals are 95% Clopper-Pearson; COVID-19 cases notified from 1 March 2020 to 1 March 2022, PIMS-TS cases from 1 May 2020 to 30st April 2022.

who had an earlier access to vaccination from Quarter 3, 2021. It is therefore also unlikely that vaccination has contributed substantially to the observed change in MIS-C rate during the Omicron waves as most cases occurred prior to high vaccine coverage in this age group. We did not observe any age-specific reduction in PIMS-TS case counts associated with the Omicron variant (Supplementary Table). Our findings support a contention that changes in viral antigens likely contributed to reduction in MIS-C incidence. Potential alteration in super-antigen-like features of the Spike protein is one possibility that requires further investigation.[5,10]

Our analysis has some limitations. Few cases had individual SARS CoV-2 genomic analysis, but the dominance of the Omicron VoC was evident in early December 2021. Further, PAEDS undertakes sentinel site surveillance. Although our network of hospitals includes >80% of tertiary pediatric beds in Australia, incomplete case ascertainment may impact the numerator in our analysis. We expect a majority of cases would have either presented or been referred to tertiary centres given MIS-C severity, frequent diagnostic uncertainty and need for acute paediatric cardiology assessment. Supporting this, through our wider clinical networks we are aware of only a relatively small number of MIS-C cases that presented outside our hospitals (PAEDS investigators, personal correspondence). Additionally, whilst Australia has had a high population level of SARS-COV-2 infection ascertainment, accuracy of infection notification rates reduced from late 2021. This was due to transiently reduced access to PCR and rapid antigen testing (RAT), changing guidelines regarding testing and voluntary or non-reporting of RAT results depending on jurisdiction, as well as reduced sensitivity of RAT. However, we suggest that increased under-reporting of infections in notification data over time would bias to overestimation of MIS-C rates in 2022 relative to 2020-21, contrasting with the observed reduction in MIS-C rates.

Contributors

A/Prof Britton and A/Prof Wood conceptualized and designed the study, were PAEDS principle investigators and attended a majority of review panel meetings, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Lopez and Dr Glover conceptualized and designed the study, performed the analysis, drafted the initial manuscript, and reviewed and revised the manuscript.

Prof Burgner, Dr Carr, A/Prof Clark, Dr Boast, Dr Vasilunas, Dr McMullan, A/Prof Francis, A/Prof Bowen, A/Prof Blyth, Prof Macartney, A/Prof Crawford were PAEDS principle investigators, attended a majority of review panel meetings and reviewed and revised the manuscript.

Ms Carey coordinated and supervised data collection and acted as secretariat for the review panel meetings.

All authors critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of interests

Dr David Burgner reports an Investigator grant from the National Health and Medical Research Council and voluntary position at the Kawasaki Disease Foundation, Australia. Dr Asha C. Bowen reports an Investigator grant from the National Health and Medical Research Council and is Vice President of the World Society of Pediatric Infectious Diseases. The rest of the authors have no conflicts of interest relevant to this article to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100604.

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