

Multisystem inflammatory syndrome in the context of paediatric COVID-19 infection in the Republic of Ireland April 2020 to April 2021

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Abstract

Aim: Our aim was to describe the epidemiology of multisystem inflammatory syndrome in children (MIS-C) in the Republic of Ireland, in the context of all cases of COVID-19 in children, during the first year of the SARS-CoV-2 pandemic.

Methods: Cases of MIS-C were identified by prospective surveillance in Irish hospitals from April 2020 to April 2021. Paediatric COVID-19 cases and outbreaks in schools or childcare facilities were notified to and routinely investigated by Public Health. Univariate and bivariate analyses were carried out in Excel, Stata and JMP statistical package.

Results: Fifty-four MIS-C cases (median age 7.58 years; males 57%) were identified over the study period. MIS-C incidence was higher in certain ethnicities ('black' 21.3/100,000 [95% CI 4.3–38.4]; and 'Irish Traveller' 14.7/100,000 [95% CI –5.7–35.1]) than those of 'white' ethnicity (3.4 /100,000). MIS-C cases occurred in three temporal clusters, which followed three distinct waves of community COVID-19 infection, irrespective of school closures. Formal contact tracing identified an epidemiological link with a COVID-19-infected family member in the majority of MIS-C cases (77%). In contrast, investigation of COVID-19 school outbreaks demonstrated no epidemiological link with MIS-C cases during the study period.

Conclusion: Efforts at controlling SARS-CoV-2 transmission in the community may be a more effective means to reduce MIS-C incidence than school closures. Establishing a mandatory reporting structure for MIS-C will help delineate the role of risk factors such as ethnicity and obesity and the effect of vaccination on MIS-C incidence.

KEYWORDS

coronavirus disease 2019, Kawasaki disease, Multisystem inflammatory syndrome in children, Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2

Abbreviations: CHI, children's health Ireland; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HSE, health service executive; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; PICU, paediatric intensive care unit; PID, paediatric infectious diseases; PIMS-TS, paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; ROI, Republic of Ireland.

1 | INTRODUCTION

While children are now considered as susceptible to SARS-CoV-2 infection as adults, they constitute a very small proportion of COVID-19 cases, admissions to hospital and intensive care, or deaths.¹⁻³ However, emergence of a potentially life-threatening hyperinflammatory syndrome associated with preceding SARS-CoV-2 infection – Multisystem Inflammatory Syndrome in Children (MIS-C) or Paediatric Inflammatory Multisystem Syndrome Temporarily associated with SARS-CoV-2 (PIMS-TS) has led to understandable concern.⁴⁻⁸ We describe the epidemiology, clinical characteristics, treatment, and outcomes of children with MIS-C in Ireland, in the context of all cases of COVID-19 in children, during the first year of the SARS-CoV-2 pandemic from April 2020 to April 2021.

2 | METHODS

From April 2020 until April 2021, we conducted prospective surveillance of patients treated for MIS-C in hospitals in the Republic of Ireland (ROI). Children's Health Ireland (CHI) at Crumlin and Temple Street provides the national paediatric infectious diseases (PID), cardiology and intensive care service (PICU) for children in Ireland. As such, paediatricians throughout the country customarily transfer or discuss cases of MIS-C with the CHI PID, cardiology, or PICU services. Medical records of all children diagnosed and treated for MIS-C in CHI were entered prospectively into a standardised electronic database. Data from children treated in other paediatric centres were obtained retrospectively. The Royal College of Paediatrics and Child Health case definition of MIS-C was used: a child with persistent fever, inflammation and organ failure (including children fulfilling criteria for Kawasaki disease), the exclusion of any other microbial cause, and positive or negative SARS-CoV-2 testing.⁹ Children diagnosed subsequently with any other microbial cause or condition were excluded from the final MIS-C group and analysed separately. Over the study period, laboratory-confirmed community COVID-19 paediatric cases and outbreaks in schools or childcare facilities were notified to and routinely investigated by Public Health Services to determine if there was any epidemiological link to a previous case of COVID-19 and to identify further cases in the facility. Deprivation scores of MIS-C and community paediatric COVID-19 cases were calculated by the Health Service Executive's (HSE) National Health Intelligence Unit based on the 2016 Haase and Pratscke (HP) Deprivation Index.¹⁰ Briefly, the HP index uses a geo-referencing tool interfaced with the postal address (www.healthatlasireland.ie) and factor analysis of three dimensions of routinely collected census data (demographic profile, e.g. age profile of population, mean number of persons per room; social class composition, e.g., percentage of population in that area with primary education only, percentage of households headed by a semi- or unskilled worker; and labour market situation, e.g., male and female unemployment, percentage of households with children under

Key Notes

- In the Republic of Ireland, the majority of cases of COVID-19 and Multisystem Inflammatory Syndrome in Children occurred in those of “white” ethnicity, but the incidence was highest among “black”, “Irish traveller”, or “other non-white” ethnicities.
- Irrespective of school closures, MIS-C cases followed surges of COVID-19 in the community where the most common epidemiological link was to a COVID-19 infected family member.
- Targeting community SARS-CoV-2 transmission may be a more effective means to reduce MIS-C incidence.

15 years with a single parent) to measure affluence/deprivation at the small area level (approximately 100 households).¹⁰ This work was undertaken under Public Health legislation (Infectious Disease Regulations 1981 and subsequent amendments¹¹). Bivariate and multivariate statistical analysis including analysis of variance (ANOVAs), Fisher's exact, Wilcoxon comparison of medians, and Pearson's 2 and the calculation of means and median were carried out in Excel and JMP statistical package.¹² Incidence rates were calculated using the 2016 census population with 95% confidence intervals, and the *p* value set at the 0.05 level. The Kaplan–Meier survival analysis was carried out in Stata statistical package.

3 | RESULTS

Sixty-three patients were diagnosed and treated for MIS-C during the study period. Nine patients were subsequently excluded because of an alternative microbiologic or clinical diagnosis. Alternative diagnoses included acute disseminated encephalomyelitis; group A streptococcal toxic shock; herpetic stomatitis; left ventricular non-compaction; periodic fever; ulcerative colitis; urosepsis; *Staphylococcus aureus* septic arthritis, and sepsis. The remaining 54 MIS-C cases form the basis of the study. Fifty-one (94.5%) cases were treated in CHI, and 3 (5.5%) were treated exclusively in other paediatric centres.

3.1 | Patient demographics

Median age of MIS-C cases was 7.6 years (range, 4 months–15.5 years) and 31 (57%) were males (Table 1). Thirty-four (63%) cases had features of inflammatory-type MIS-C and 20 (37%) fulfilled criteria for complete or incomplete Kawasaki disease (KD). Kawasaki Disease-type MIS-C cases were significantly younger (median 2 years; range, 0.3–11 years) than those with inflammatory-type MIS-C (median, 9.5 years; range, 2–15.5 years, $p < 0.00001$). There were more girls (12/20; 60%) among MIS-C cases in the 0–4-year

age group and more boys in the 5–12 year (19/30; 63.3%) and 13–15 year age groups (3/4; 75%) (Pearson's χ^2 , 3.3, $p = 0.19$) (Table 2). In contrast, no difference was evident in age distribution or gender among COVID-19 cases diagnosed in the community, hospitalised, or admitted to PICU during the same timeperiod (Fisher's exact test; $p = 0.29$). The majority of MIS-C patients were previously healthy; four children had mild asthma, two reported mild eczema, and one child had a diagnosis of Asperger's syndrome. Twenty-one (44%) of 48 patients with documented measurements had bodyweight ≥ 91 st percentile for age. Only two patients had bodyweight below the ≤ 10 th percentile for age.

3.2 | Clinical presentation

All MIS-C cases had fever on presentation (Table 1). Gastrointestinal symptoms were common (81%), while respiratory symptoms were relatively uncommon (20.4%). Rash was present in 72%, conjunctivitis in 57%, and mucous membrane involvement and lymphadenopathy in 41% and 37%, respectively.

3.3 | Echocardiography

Twenty-five of 50 (50%) MIS-C cases had an echocardiographic abnormality at presentation, impaired myocardial contractility,¹² coronary artery ectasia¹¹ and dilatation,⁶ and myocarditis.⁶ Impaired myocardial contractility and/or myocarditis were more common among inflammatory-type MIS-C cases (50%, 16/32 vs. 5%, 1/18), whereas coronary artery abnormality was more common among KD-type (42%; 8/19) MIS-C cases versus

inflammatory-type (28%; 9/32). All but three cases (coronary artery dilatation, 2; ectasia, 1) had normal echocardiograms at follow-up (median 2 months), with the majority returning to normal within a few days of presentation.

3.4 | Laboratory results

Laboratory results were recorded on admission and days 3 and 5 of hospitalisation. Lymphopenia and elevation of CRP and D-Dimers were characteristic at presentation. In summary, lymphocyte counts were significantly lower ($0.8\text{--}2.8 \times 10^9$ $p = 0.0003$), and platelet counts significantly higher ($187\text{--}437 \times 10^9$ $p = 0.0004$) among inflammatory-type MIS-C cases than KD-type cases on admission and through day 5 of hospitalisation. Cardiac biomarkers were elevated in 26 of 44 (59%) MIS-C patients, again more commonly among inflammatory- (21/30, 70%) than KD-type (5/14, 35.7%) MIS-C cases. C-reactive protein levels were not significantly different among inflammatory and KD-type MIS-C cases (122 – 129 mg/L, $p = 0.25$).

3.5 | SARS-CoV-2 infection status

Twenty-nine (54%) MIS-C patients had evidence of previous SARS-CoV-2 infection (SARS-CoV-2 PCR and/or IgG positive). Seventeen of 54 (31.4%) MIS-C cases were SARS-CoV-2 PCR-positive on hospital admission⁹ or in the community prior to admission.⁸ SARS-CoV-2 IgG was positive in 19 of 38 patients (50%). Interestingly, 72% of inflammatory-type MIS-C cases were SARS-CoV-2 IgG seropositive compared to only 8% of KD-type (Table 1).

TABLE 1 Demographic and SARS CoV-2 exposure according to MIS-C subtype

	MIS-C n = 54	Inflammatory-type MIS-C n = 34	KD-type MIS-C n = 20
Male	31 (57%)	24 (71%)	7 (35%)
Female	23 (43%)	10 (29%)	13 (65%)
Median age in years (range)	7.58 (0.3–15.5)	9.5 (2.1–15.5)	2 (0.3–11)
SARS CoV-2 PCR positive	17/54 (31%)	14/34 (41%)	3/20 (15%)
SARS CoV-2 IgG positive	19/38 (50%)	18/25 (72%)	1/13 (8%)
SARS CoV-2 PCR and/or IgG positive	29 (54%)	26 (76%)	3 (15%)

TABLE 2 Sex and age distribution of MIS-C and community paediatric COVID-19

Age group (years)	MIS-C cases					Community COVID-19 cases				
	Females	%	Males	%	Total	Females	%	Males	%	Total
0–4	12	60%	8	40%	20	3887	48.52%	4123	51.47%	8010
5–12	11	36.6%	19	63.3%	30	6803	49.23%	7015	50.77%	13,818
13–16	1	25%	3	75%	4	4435	50%	4435	50%	8870
Total	24	44.4%	30	55.6%	54	15,125	49.27%	15,573	50.72%	30,698

3.6 | Treatment and outcome

The majority of MIS-C cases received immunomodulatory treatment with intravenous immunoglobulin (98%) and/or steroids (82%). None received antiviral or interleukin inhibitor treatment. Median length of hospital stay was 7 days (range, 3–29 days). Thirteen (26%) MIS-C cases required PICU admission (median length of stay, 3-days; range, 1–6 days). Over half of patients (55%) required IV fluid resuscitation on presentation, nine (17%) received inotropic support, and 2 (4%) required conventional mechanical ventilation. None required extracorporeal membrane oxygenation or renal replacement therapy. Rates of PICU admission (34.4% vs. 11.1%), mechanical ventilation (6.25% vs. 0%), and inotropic support (18.7% vs. 5.5%) were higher among inflammatory type-MIS-C cases than KD-type. Rates of PICU admission decreased as the pandemic progressed; 3/3 were admitted to PICU in the first wave; 4/6 in the second wave; and 5/25 in the third wave. There was one case of transient cardiac arrest but no myocardial infarctions or fatalities among our MIS-C cohort, and all patients were discharged home.

3.7 | Ethnicity

Cumulative incidence of MIS-C during the study period was 4.8 per 100,000 population aged 0–16 years. The largest proportion of cases of MIS-C was in children and adolescents of ‘white’ ethnicity; however, the corresponding incidence per population (0–16 years) was lower (3.4/100,000) than all other ethnic groups, with the exception of children of ‘Chinese’ ethnicity who had no cases. However, proportions of MIS-C cases among children of ‘other’, (24.7/100,000) ‘black’ (21.4/100,000), or ‘Irish traveller’ (14.7/100,000) ethnicity exceeded their respective proportions of the total 0–16-year population (Table 3).

Cumulative incidence of COVID-19 was 2733 cases /100,000 population aged 0–16 years for the study period. The incidence of COVID-19 also varied by ethnicity. While children and adolescents of ‘white’ ethnicity constituted the largest proportion of paediatric COVID-19 cases, children and adolescents of ‘Irish Traveller’ ethnicity had the highest incidence of COVID-19 infection at 11,127 cases /100,000 population aged 0–16 years. Over the course of the study period, incidence of MIS-C was 1.76 /1000 children with confirmed SARS-CoV-2 infection (54 of 30,701) and 4.8 cases /100,000 children within the entire paediatric population.

3.8 | Geographic distribution and deprivation index

Multisystem inflammatory syndrome in children cases occurred throughout the country, with the majority (42.5%, 23/54), not unexpectedly, living in the most populous Eastern region, which also had the highest incidence of COVID-19. The lowest incidence of MIS-C was reported in the southern region, the area with lowest incidence of COVID-19 infection. Deprivation scores for all 54 MIS-C cases

TABLE 3 Incidence of MIS-C and community paediatric COVID-19 according to ethnicity

Ethnicity	ROI population 0–16 years	Number of MIS-C cases	Percent of total MIS-C cases	Incidence per 100k population aged 0–16	Lower 95% CI	Upper 95% CI	Number of COVID-19 cases 0–16 years	Percent of total COVID-19 cases	Incidence per 100k population aged 0–16	Lower 95% CI	Upper 95% CI
White	89.1%	34	63%	3.4	2.3	4.5	20,526	67%	2050.9	2023.1	2078.6
Irish Traveller	1.2%	<5 ^a	4%	14.7	-5.7	35.1	1515	5%	11127.4	10599.2	11655.7
Black	2.5%	6	11%	21.4	4.3	38.4	910	3%	3238.3	3031.4	3445.3
Chinese	0.4%	0	0%	0.0	0.0	0.0	71	0%	1563.9	1203.0	1924.8
Other ^b	4.3%	12	22%	24.7	10.8	38.8	2331	8%	4807.7	4617.3	4998.1
Unknown	2.5%	0	0%	0.0	n/a	n/a	5348	17%	n/a	n/a	n/a
Total	100%	54	100%	4.8	3.5	6.1	30,701	100%	2732.8	2702.7	2763.0

Note: Ethnicity was available for 83% (n = 25,353) of paediatric COVID-19 cases (age 0–16 years) reported during this time; ethnicity was not known or not specified for the remaining 17% (n = 5348) of cases. Ethnicity was available for all patients with MIS-C. Population taken from 2016 census for population aged 0–16 years (1,123,409 children).¹³

^aIn order to protect patient confidentiality and comply with Irish Statistical Disclosure Control Guidance, patient groups containing <5 cannot be reported.

^b‘Other’ includes those who are not among the abovementioned ethnic groups (White, Irish Traveller, Black, Chinese) and those of mixed ethnicity.

demonstrated 70% (95% CI 57.1–81.8) (38/54) occurred in areas of average deprivation; 18.5% (95% CI 10.4–30.8) (10/54) in more deprived areas and 11% (95% CI 5.2–22.2) (6/54) in more affluent areas. Differences in percentage of cases among the deprived and affluent categories over the entire study period or between waves 1 and 3 of the pandemic were not statistically significant.

3.9 | Epidemiologic link to person with COVID-19 infection

Systematic formal contact tracing detected an epidemiologic link with a COVID-19-infected individual in 50%¹⁴ of MIS-C cases; most commonly close contact with a family member (77%, 21) rather than a social (11%, 3) or school/childcare facility (7%, 2) contact. Median time from close contact with a confirmed case to presentation with MIS-C was 35 days (range, 14–109 days). Kaplan Meier analysis of time to presentation with MIS-C or by MIS-C type from time of confirmation as a confirmed COVID-19 case or a close contact was not significantly different. However, time to presentation with MIS-C from time of diagnosis as a confirmed COVID-19 case or a close contact was significantly different among different ethnicities (Figure 1). Time to presentation with MIS-C from time of confirmation as a COVID-19 case or close contact was earliest among those of 'Irish traveller' and 'black' ethnicity and longest in those of 'white Irish' ethnicity.

3.10 | Timing of presentation of MIS-C cases in relation to community COVID-19 activity, school closures and school COVID-19 outbreaks

Multisystem inflammatory syndrome in children cases occurred in three temporally distinct clusters over the course of the study: May–June 2020; October–November 2020; and January–March 2021 (Figure 2). Clusters of MIS-C cases occurred consistently after the

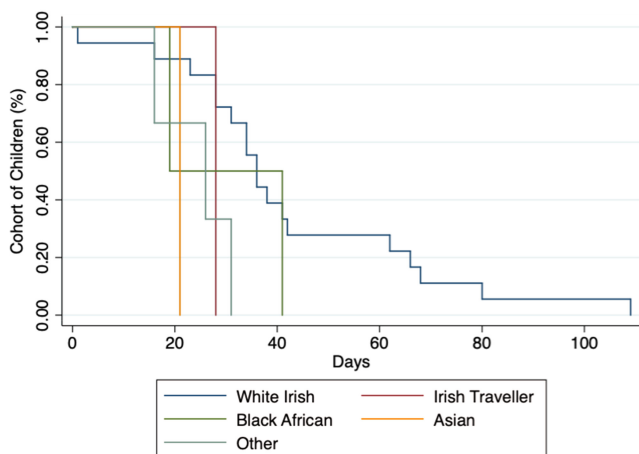


FIGURE 1 Time from COVID-19 case or close contact to MIS-C presentation by ethnicity.

increase and peak in community COVID-19 infections (Figure 2). In contrast, the temporal relationship between MIS-C cases and school and childcare facilities closures is less clear; only one of three MIS-C clusters (the smaller October peak) occurred at a time when schools and child-care facilities were still open. Furthermore, during the study period, systematic prospective Public Health investigation of all community paediatric COVID-19 cases and school outbreaks nationally and retrospective investigation following MIS-C case presentations did not identify an epidemiologic link.

4 | DISCUSSION

We describe 54 children (aged between 4 months and 16 years) diagnosed and treated for MIS-C over the course of a year (April 2020 to April 2021) following the first descriptions of this new clinical condition. Clinical features, laboratory results, and echocardiography were comparable to larger case series reported from the United Kingdom and United States.^{5,6,15–19} Similarly, the majority of our MIS-C cases had preceding history of gastrointestinal symptoms with only a minority reporting respiratory symptoms.^{17,18} While most of our cases occurred in otherwise healthy children, we do note that 44% of our MIS-C cohort had a body weight above the 90th percentile which highlights again the increased risk of severe COVID-19 in patients with obesity.^{8,20} All cases were successfully treated with IVIG and steroids without recourse to interleukin inhibitors. Fewer of our MIS-C cases required PICU admission (26%), inotropic support (13%), or mechanical ventilation (4%) than earlier UK and US series (44%–80%; 30%–50%; and 20%–16%, respectively), and there were no fatalities.^{6,15,17,18,20} Notwithstanding potential variability in PICU admission criteria and bed capacity, reduced severity of illness and more favourable outcomes in our MIS-C cohort may reflect increased awareness of the condition, treatment earlier in the course of the illness, and the benefit of experience of other centres. The majority of our MIS-C cases presented later (January–February 2021) than those reported in the UK and US (April–May 2020), by which time diagnostic criteria and treatment protocols were better established. Alternatively, it is conceivable that COVID-19 vaccination of adults, which began in Ireland at the end of December 2020, may have had an indirect beneficial effect on severity of COVID-19 and /or MIS-C in Irish children.

Fourteen per cent (9/63) of our cases (some of whom were SARS-COV-2 PCR and/or antibody positive) fulfilled diagnostic criteria and were treated as MIS-C but subsequently had another diagnosis. This emphasises the inherent difficulty in diagnosis and the need for appropriate empiric antimicrobial treatment in the early stage of the illness, repeat clinical examination and investigation, and multidisciplinary care. In the continuing absence of a diagnostic test, the need for more specific diagnostic criteria and ongoing research into biomarkers to aid diagnosis and treatment of MIS-C is clear. This is particularly true for KD-type MIS-C cases, which may be difficult to distinguish from normal background KD cases. One-third of our MIS-C cohort fulfilled criteria for KD and were younger

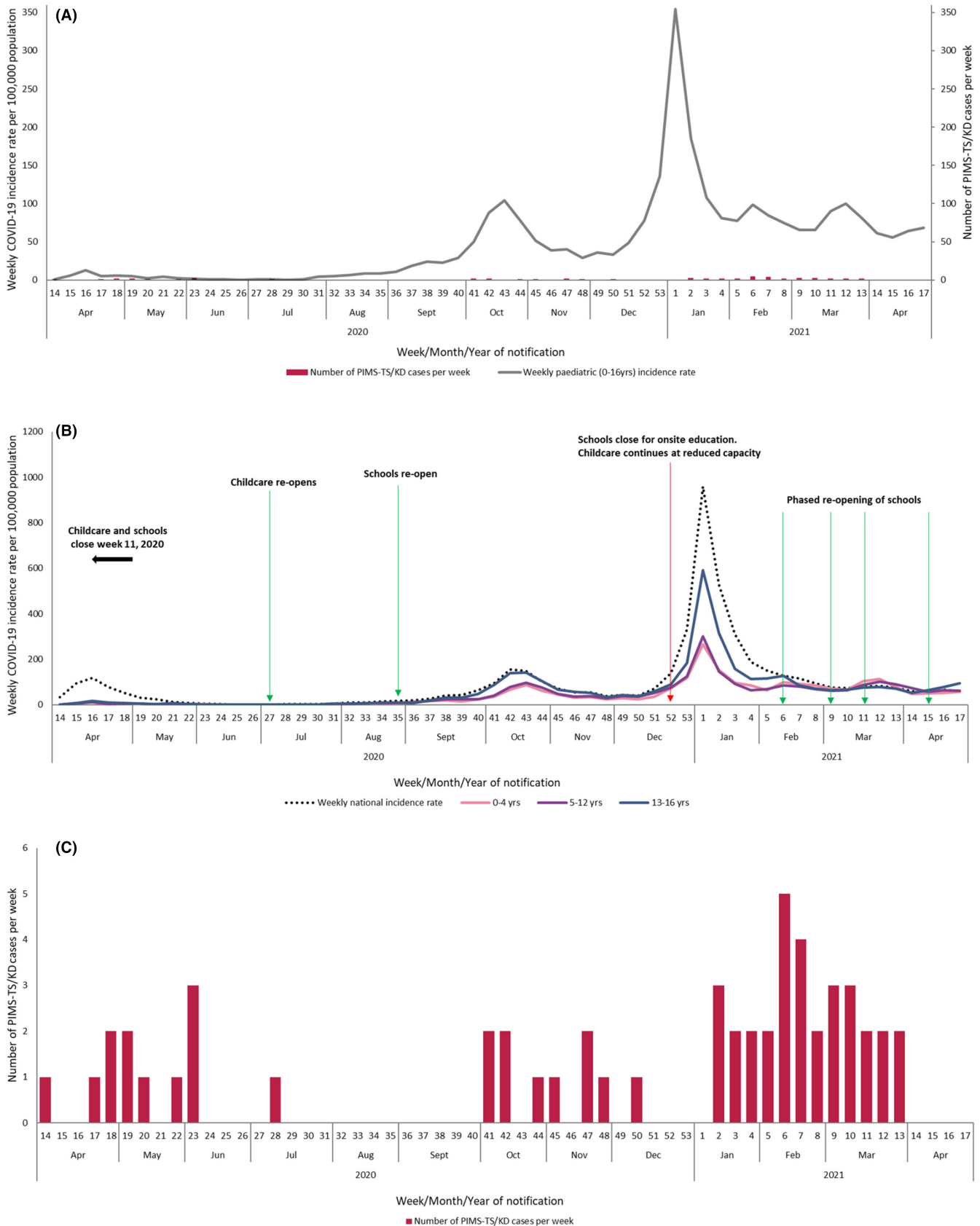


FIGURE 2 (A) Weekly incidence rate of paediatric cases against weekly number of PIMS-TS/KD cases. (B) Weekly incidence of community paediatric COVID-19 cases by age group against daily national incidence rate with key dates for school opening and closures. (C) Weekly number of MIS-C cases ($n = 54$).

(median, 1.75 years), more likely to be female (60%), and less likely to require steroid treatment, PICU admission, inotropic support, or ventilation than those with inflammatory-type MIS-C. Interestingly, while the SARS-CoV-2 seropositivity rate (72%) among our older (inflammatory-type) MIS-C cases was comparable with that of other larger series,²¹ only a small minority (8%) of our KD-type cases were SARS-CoV-2-seropositive. While this may be a consequence of our sample size, it raises the possibility that some of our MIS-C cases may have represented background KD activity during the pandemic and warrants further investigation.

As noted elsewhere, ethnicity appeared to have a major influence on incidence of MIS-C in our cohort. Irish children and adolescents of 'non-white', 'black', or 'Irish traveller' ethnicity were over-represented in both our MIS-C and community COVID-19 cases,²²⁻²⁴ relative to their proportion of the paediatric population. Interestingly, the interval from time of infection to developing MIS-C varied significantly across different ethnicities with 'black' and 'Irish traveller' children and adolescents presenting earlier than those of 'white' Irish ethnicity. Furthermore, in contrast to their well-described predisposition for KD, children of 'Chinese - Asian' ethnicity were notably absent among our MIS-C cases. Ongoing surveillance and analysis of larger data sets is required to further investigate ethnicity as a risk factor for MIS-C in our population.

Multisystem inflammatory syndrome in children cases were concentrated, not unexpectedly, in the most populous areas of the country. However, in contrast to the recently described association between deprivation and community COVID-19 infection, the higher proportion of MIS-C cases noted among children from deprived areas in our study did not achieve statistical significance.^{24,25} Further study on a larger cohort of children may be required to determine if our findings reflect our small sample size.

Contact tracing identified an antecedent close-contact with a confirmed COVID-19-positive individual (most commonly household contact with a family member) as the most frequent epidemiologic link to infection in 46% of our MIS-C cases. Despite investigation of all COVID-19 outbreaks in schools, no epidemiologic link was found to our cohort of MIS-C cases.

Our study has a number of limitations. Firstly, notwithstanding that CHI is the national referral centre for PID, paediatric cardiology, and PICU, it is possible that MIS-C cases treated elsewhere may not have been recorded. In the absence of a positive SARS-CoV-2 PCR result, MIS-C is not yet a notifiable condition in the ROI. In addition, because records of MIS-C cases diagnosed and treated in centres other than CHI were collected retrospectively, and complete clinical and laboratory data were unavailable for a small number of patients. Secondly, unavailability of paediatric echocardiography in other centres may have resulted in underestimation of the proportion of cases with compromised cardiac function on presentation. Thirdly, given the frequency of gastrointestinal symptoms in our cohort, reliance on results of SARS-CoV-2 testing from respiratory specimens alone may have reduced the number of cases with laboratory-confirmed SARS-CoV-2 infection. And finally, whilst all Covid-19 cases who were infectious whilst attending school or childcare facilities were

followed by Public Health to ensure exclusion and testing of close contacts, it is possible that not all MIS-C cases linked to outbreaks in schools or childcare facilities were identified.

In conclusion, in the first year of the COVID-19 pandemic in the ROI, MIS-C followed surges of COVID-19 infection in the community irrespective of school and childcare facility closures. Contact tracing of MIS-C cases most commonly identified an epidemiologic link to close household contact with a COVID-19-infected family member rather than to contacts in schools or childcare facilities. In addition, investigation of all school COVID-19 outbreaks failed to demonstrate an epidemiologic link to our MIS-C cohort. Decisions around school and childcare facility closures to control the COVID-19 are complex and nuanced. However, our findings support the consensus that such measures be used as a last resort and that controlling SARS-CoV-2 transmission in the community may be a more effective means to reduce MIS-C incidence.^{26,27} COVID-19 vaccination of adolescents began in the ROI in August 2021. Mandatory reporting and ongoing surveillance of paediatric COVID-19 and MIS-C cases will help determine the long-term impact of vaccination on incidence and severity and identify those at greatest risk of MIS-C in our paediatric population.^{14,28}

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

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