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REGULAR ARTICLE

Multisystem inflammatory syndrome in children rose and fell with the first wave of the COVID-19 pandemic in France

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Abstract

Aim: This study determined the influence of the COVID-19 pandemic on the occurrence of multisystem inflammatory syndrome in children (MIS-C) and compared the main characteristics of MIS-C and Kawasaki disease (KD).

Methods: We included patients aged up to 18 years of age who were diagnosed with MIS-C or KD in a paediatric university hospital in Paris from 1 January 2018 to 15 July 2020. Clinical, laboratory and imaging characteristics were compared, and new French COVID-19 cases were correlated with MIS-C cases in our hospital.

Results: There were seven children with MIS-C, from 6 months to 12 years of age, who were all positive for the virus that causes COVID-19, and 40 virus-negative children with KD. Their respective characteristics were as follows: under 5 years of age (14.3% vs. 85.0%), paediatric intensive care unit admission (100% vs. 10.0%), abdominal pain (71.4% vs. 12.5%), myocardial dysfunction (85.7% vs. 5.0%), shock syndrome (85.7% vs. 2.5%) and mean and standard deviation C-reactive protein (339 ± 131 vs. 153 ± 87). There was a strong lagged correlation between the rise and fall in MIS-C patients and COVID-19 cases.

Conclusion: The rise and fall of COVID-19 first wave mirrored the MIS-C cases. There were important differences between MIS-C and KD.

KEYWORDS
COVID-19, Kawasaki disease, multisystem inflammatory syndrome, pandemic, PIMS

Abbreviations: COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; PIMS-TS, paediatric multisystem inflammatory syndrome temporally associated with COVID-19; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

1 | BACKGROUND

More than one million people have died since the start of the COVID-19 pandemic,[1] but children have been relatively spared, in terms of both the incidence of the disease and the severity. Patients under 20 years of age have been reported to represent less than 2.0% of patients.[2] However, on 27 April 2020, the UK National Health Service issued an alert after a small number of children presented with an inflammatory syndrome related to COVID-19. These children were extremely ill and had similar features to atypical Kawasaki disease (KD), toxic shock syndrome[3] and KD shock syndrome.[4] The UK Royal College of Paediatrics and Child Health defined these cases as paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).[3] The US Centers for Disease Control and Prevention immediately defined it as multisystem inflammatory syndrome in children (MIS-C)[5] and the World Health Organization (WHO) named it multisystem inflammatory syndrome in children and adolescents, temporally related to COVID-19.[6] In May and June 2020, reports from Italy,[7] the UK,[4,8] France,[9,10] Spain,[11] Switzerland[12] and the United States[13–16] described groups of children fulfilling these descriptions. These reports used different terminologies: MIS-C, PIMS-TS, Kawasaki-like disease or a combination of these. The announcement of this syndrome has raised important global concerns in the public and, in particular, among parents.

It has not been clearly demonstrated that this inflammatory condition is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that results in COVID-19. However, the temporal associations described in different countries, and the confirmation of the SARS-CoV-2 infection in most patients presenting with this inflammatory condition, provide a strong argument that they are linked.[17,18] The reports from different countries have described some differences, but they have also pointed out some similarities between these patients and patients with KD. Relatively, few patients have been reported to date and that is why more data are needed on this syndrome, for a deeper insight into this condition and to better understand the local kinetics of the evolution of the COVID-19 pandemic and the occurrence of MIS-C.

We observed an outbreak of MIS-C in our paediatric university hospital in Paris, as in many other centres, during the first wave of the COVID-19 pandemic. This study had two aims. The first was to describe the kinetics of the MIS-C cases and the COVID-19 pandemic in France, in order to determine whether they were related and what influence the pandemic had on MIS-C cases. The second was to describe the clinical, laboratory, echocardiographic and imaging characteristics of the children involved in this MIS-C outbreak, who were all tested positive for SARS-CoV-2, to patients with KD.

Key Notes

- France saw a strong lagged correlation between the rise and fall of multisystem inflammatory syndrome (MIS-C) in children and the first wave of COVID-19.
- The study also compared seven children with MIS-C, who were all positive for the virus that causes COVID-19, and 40 with Kawasaki disease who did not have the virus.
- The authors concluded that MIS-C patients clearly demonstrated a different clinical picture to patients with Kawasaki disease.

2 | METHODS

2.1 | Patients and definitions

We retrospectively reviewed the records of all patients up to 18 years of age who had been admitted to the University Pediatric Hospital Armand Trousseau in Paris with a diagnosis of KD or Kawasaki-like disease from 1 January 2018 to 15 July 2020. The paediatric emergency department in this tertiary paediatric hospital is visited by 55,000 patients a year. Children and adolescents fulfilling the MIS-C,[5] PIMS-TS[3] or WHO[6] definitions of an inflammatory multisystem syndrome were also included. KD is an acute vasculitis of unknown origin that presents as a febrile illness and predominantly affects children under 5 years of age. Diagnosis was based on the clinical criteria described in the 2017 guidelines issued by the American Heart Association.[19] Patients who meet the case definition are said to have complete KD, namely typical or classic KD, whereas those who do not have sufficient principal clinical findings may be diagnosed with incomplete or atypical KD.[19] The diagnosis of classic KD is based on fever for five or more days, together with at least four of the five principal clinical features. These are as follows: (a) oral changes, including erythema, cracked lips, a 'strawberry tongue' and diffuse erythema of the oropharyngeal mucosa, (b) a bilateral bulbar conjunctival infection, (c) erythematous rash, (d) erythema and oedema of the hands and feet and (e) cervical lymphadenopathy of at least 1.5 cm in diameter. If coronary artery abnormalities are detected, the diagnosis of KD is considered to be confirmed in most cases.[19] Other clinical, laboratory and echocardiographic findings can support the diagnosis of incomplete KD if a patient's clinical presentation suggests KD, but their clinical features do not meet the epidemiological case definition. KD shock syndrome has been defined by Kanegaye et al[20] as: initiation of volume expansion and infusion of vasoactive agents or transfer to intensive care due to systolic hypotension for age or a decrease of at least 20% in systolic blood pressure from baseline or clinical signs of poor perfusion.

Multisystem inflammatory syndrome in children cases have been defined in three ways by the US Centers for Disease Control and Prevention[5]: first, a patient under the age of 21 years presenting with fever, laboratory evidence of inflammation, evidence of clinically severe illness requiring hospitalisation and the involvement of two or more organs, namely cardiac, renal, respiratory, haematological, gastrointestinal, dermatological or neurological; second no alternative plausible diagnoses; and third being positive for current or recent SARS-CoV-2 infections or COVID-19 exposure in the 4 weeks before the onset of symptoms. Some of

these patients may fulfil all, or some, of the criteria for Kawasaki disease.[5] The comparisons of the MIS-C, PIMS-TS and WHO definitions are shown in Table S1.

2.2 | Data collected

Data on patient demographics, clinical, laboratory, echocardiographic, imaging, therapeutic, and outcomes were collected for patients seen from 1 January 2018 to 15 July 2020. We collected data using a standardised form from both the hospital's electronic health record system and paper health records. For patients seen from 1 April 2020 to 15 July 2020, we collected data on SARS-CoV-2 infections and close COVID-19 contacts and determined whether patients fulfilled the MIS-C,[5] PIMS-TS,[3] WHO[6] definitions or the classic or incomplete KD criteria.[19] Since data collection on race and ethnicity are not allowed in France, these were not available. Although the above definitions are very similar, we chose to use the definition for MIC-S in our hospital because we felt that the link suggested with a SARS-CoV-2 infection was more straightforward, Table S1.

2.3 | Treatment

As MIS-C is a new syndrome, patients who were affected were treated according to our hospital protocol for KD. The first-line treatment was intravenous immunoglobulins at 2 g/kg as a single infusion given over 10–12 hours. If apyrexia was not obtained within 36 hours, or fever reappeared <7 days after initial treatment, the treating physician could decide on a second dose of intravenous immunoglobulins and/or the use of corticosteroids.[19]

2.4 | Detecting SARS-CoV-2

We identified SARS-CoV-2 ribonucleic acid using reverse-transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swabs or stool samples. Samples were obtained within the first 48 hours of admission. We used the Allplex nCoV assay (Seegene Inc, Seoul, South Korea) and the Bosphore v2 nCoV assay (Anatolia Geneworks, Istanbul, Turkey). We identified SARS-Cov-2 IgG antibodies using the Alinity-i SARS-CoV-2 IgG (Abbott Molecular, Illinois, USA). Serology was performed during hospitalisation for patients admitted from 1 April to 15 July 2020. Positive RT-PCR or serology results defined patients with a proven SARS-CoV-2 infection.

2.5 | Comparing MIS-C and KD patients

All the MIS-C patients had the SARS-CoV-2 infection. They were compared to KD patients, including those who did not have the viral infection during the pandemic phase of the study.

2.6 | Evolution of the pandemic and occurrence of MIS-C

To determine the relationship between the occurrence of MIS-C and the evolution of the COVID-19 pandemic in France, which had 66.5 million inhabitants in January 2020,[21] we obtained official French COVID-19 data from Public Health France. The cumulative confirmed COVID-19 cases for the whole country were collected and for every week from the beginning of the epidemic, as well as the mean daily number of new cases. These data were used to construct chronological curves that were analysed according to the occurrence of MIS-C.

In order to test the influence of the number of new COVID-19 cases in our region on the occurrence of MIS-C cases, we obtained data on COVID-19 visits to emergency departments (ED) from the Oscour surveillance network. This surveillance network automatically collects anonymous, real-time, demographic, and diagnostic data from 86% of all French emergency departments. These COVID-19 data, available at Public Health France, enabled us to calculate the daily and weekly number of COVID-19 ED visits of patients of all ages in the whole Paris region from the beginning of the pandemic and correlate them to the occurrence of MIS-C cases in children in our hospital.

2.7 | Statistical analysis

The characteristics of the two groups were compared using the Student *t* test for continuous variables and the chi-square test or Fisher's exact test, as necessary, for categorical variables. The strength of the relationship between the number of new COVID-19 cases and the number of MIS-C cases was tested with Spearman's rho correlation coefficient. A linear regression model was used to measure the extent of the explained variance. Analyses were performed with SPSS, version 18 (SPSS Inc, Chicago, USA). A p value of < 0.05 was considered statistically significant.

2.8 | Ethical approval

This study was approved by the Ethics Committee for Research of the Sorbonne University. Parents were informed that their children's data would be anonymously used and could ask for them to be excluded from the analysis; none of them did so.

3 | RESULTS

The study comprised 47 patients admitted to the hospital from 1 January 2018 to 15 July 2020. These included seven patients diagnosed with MIS-C and 40 diagnosed with KD.

3.1 | Description of the MIS-C outbreak

Between 13 April and 15 July 2020, seven children diagnosed with MIS-C and 10 children diagnosed with typical or atypical KD were admitted to our hospital. The combined incidence of MIS-C and typical and atypical KD during that period was 5.7 patients per month. In comparison, 30 children diagnosed with typical or atypical KD were admitted from January 2018 to March 2020, with a mean incidence of 1.1 patients per month. Figure 1, panel A shows all the children with typical or atypical KD and the children with MIS-C, admitted by month, and their need for a PICU stay from 1 January 2018 to 15 July 1 2020. The main characteristics of the seven MIS-C patients are shown in Table 1. There were two males aged 0.5 and 12.6 years and five females aged 5.8, 6.0, 7.5, 8.3 and 11.3 years.

All seven MIS-C patients tested positive for the SARS-CoV-2 infection: one had a positive RT-PCR from a nasopharyngeal swab and all seven had positive immunoglobulin G (IgG) serology. A known COVID-19 contact was found in five of these seven children and these are detailed in Table 2. Two of the seven children with MIS-C also fulfilled the criteria for classic KD. The use of the PIMS-TS and WHO definitions yielded the same results as the

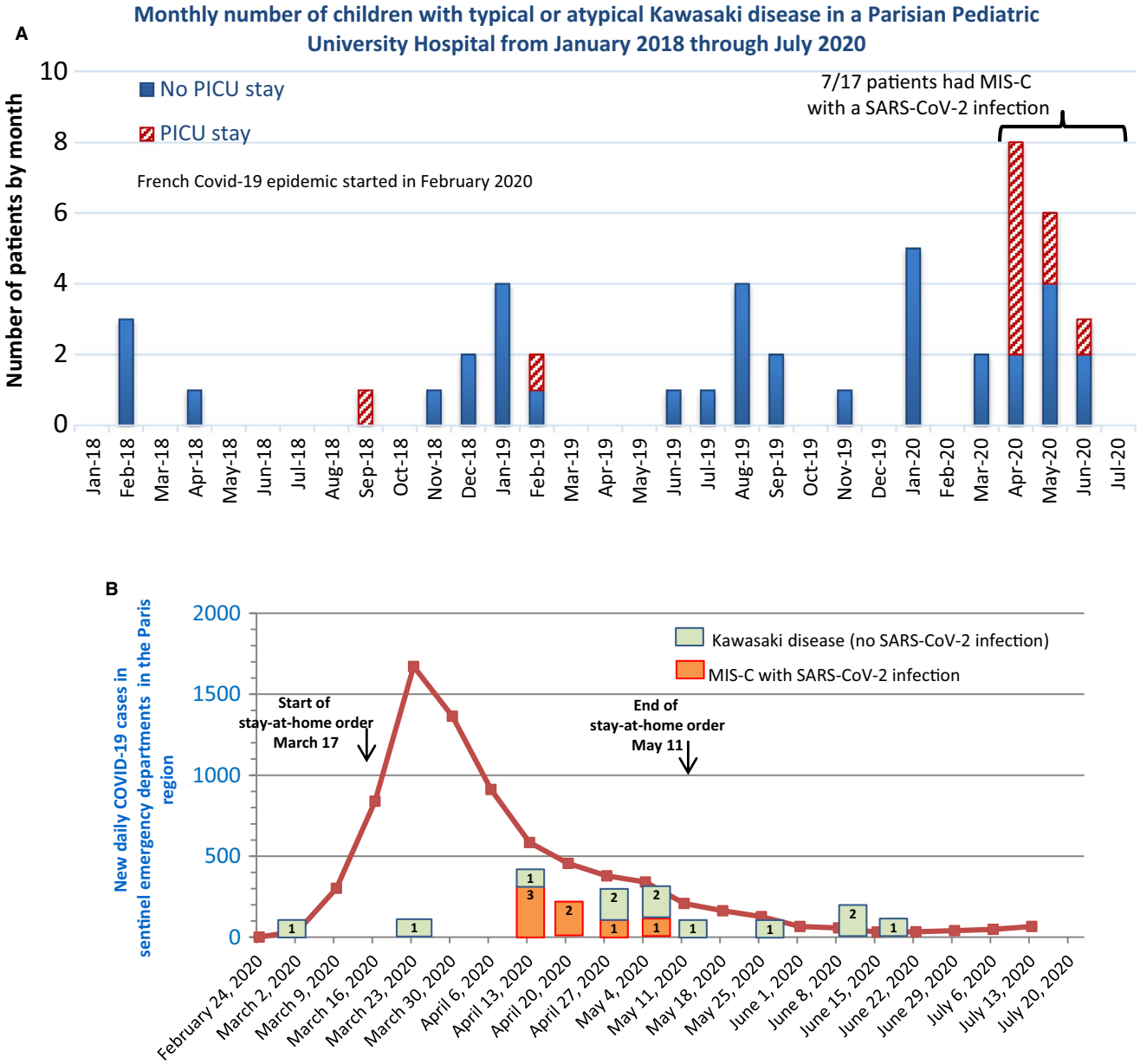

FIGURE 1 Panel A. Monthly occurrence of KD cases and MIS-C in our paediatric university hospital in Paris from January 2018 to July 2020. Red dashed bars indicate cases admitted to the paediatric intensive care unit (PICU). Panel B. Daily number of new cases of COVID-19 reported for the Paris region from March to July 2020 and the weekly number of KD, and MIS-C cases who tested positive for SARS-CoV-2, displayed by the week of occurrence, admitted to the same hospital (bars). Numbers within the bars indicate the number of patients

TABLE 1 Description of the seven children with MIS-C children who presented to the paediatric university hospital during the first wave of the COVID-19 pandemic

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Date of hospitalisation	13 April	19 April	19 April	20 April	20 April	28 April	5 May
Age (years)	8.3	12.6	5.8	11.3	0.5	6.0	7.5
Sex	Female	Male	Female	Female	Male	Female	Female
SARS-CoV-2 infection	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RT-PCR (nasal swab/ stool)	Neg/ND	Neg/Neg	Pos/ND	Neg/Neg	Neg/ND	Neg/ND	Neg/ND
Serology (IgG)	Pos	Pos	Pos	Pos	Pos	Pos	Pos
COVID-19 contact[a]	No	Yes	No	Yes	Yes	Yes	Yes
Other respiratory viruses[b]	No	No	ND	No	No	No	No
PICU stay in days	3	2	8	12	2	7	8
Met PIMS-TS definition	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Met WHO definition	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kawasaki major criteria[c]							
Type of presentation	Classic	Incomplete	Incomplete	Incomplete	Incomplete	Classic	Incomplete
Number of major criteria	4	3	3	1	3	5	2
Extremity changes	Yes	No	Yes	Yes	No	Yes	No
Rash	Yes	Yes	Yes	No	Yes	Yes	Yes
Conjunctivitis	Yes	Yes	No	No	Yes	Yes	No
Oral changes	Yes	Yes	Yes	No	Yes	Yes	Yes
Cervical lymphadenopathy	No	No	No	No	No	Yes	No
Days of fever at diagnosis	5	6	7	4	7	5	6
Other signs and symptoms							
Abdominal pain	Yes	Yes	Yes	Yes	No	No	Yes
Other	Vomiting, stiff neck	Vomiting, diarrhoea	Vomiting, diarrhoea, sterile pyuria	Vomiting	Hydrocele, irritability	Cervical pain	Vomiting, diarrhoea
Echocardiography	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Abnormal	Abnormal
Aneurism	No	No	No	No	No	No	No
Ejection fraction	25%	55%	31%	55%	70%	25%	30%
Mitral regurgitation	Yes	No	No	No	No	No	Yes
Pericardial effusion	Yes	No	No	Yes	No	No	Yes
Electrocardiography	Normal	Normal	ST segment elevation	ST segment depression	Normal	Normal	Normal
Myocardial dysfunction	Yes	Yes	Yes	Yes	No	Yes	Yes
KDSS	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chest X-ray	Normal	Normal	Right pleural effusion, Cardiomegaly	Cardiomegaly	Bilateral alveolar opacities	Cardiomegaly	Cardiomegaly, bilateral perihilar alveolar opacities

(Continues)

TABLE 1 (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Others imaging findings	Pleural effusion	Peritoneal effusion, terminal ileitis	Peritoneal effusion	Peritoneal and pleural effusion. Typical COVID-19 opacities on chest CT (subpleural areas of focal consolidation and ground glass opacities)	ND	Pleural effusion, retropharyngeal abscess on cervical CT	ND
Laboratory values[d]							
Leucocytes count/µl	16,090	9,040	19,800	6,670	1,660	4,730	22,120
Neutrophil count/µl	14,270	8,260	16,800	5,940	150	3,590	19,470
Lymphocyte count/µl	770	510	1,500	315	1,380	710	880
Haemoglobin, g/dl	8,9	13.7	8.2	7.2	7.6	10.1	7.9
Platelet count/µl	281,000	227,000	210,000	122,000	102,000	102,000	187,000
C-reactive protein, mg/L	134	340	183	315	261	310	390
Procalcitonin, ng/ml	9.83	8.62	242.44	63.51	50.79	13.08	NA
Fibrinogen, mg/dl	7.01	7.21	6.39	7.08	2.18	6.16	7.56
Ferritin, ng/ml	334	NA	NA	NA	470	NA	NA
Triglycerides, mg/dl	1.14	NA	NA	NA	1.38	NA	NA
D-dimer, ng/ml	4,407	NA	13,942	>20,000	2,660	2,604	1,416
ALT, U/L	15	38	21	46	6	<5	32
AST, U/L	29	71	115	77	11	21	62
Lipase U/L	128	153	45	168	NA	15	42
Albumin (lowest), g/L	19.7	24.5	18	19.1	21	18.4	20.6
Sodium (lowest), mEq/L	128	129	133	136	133	130	123
LDH, U/L	487	581	337	NA	300	NA	NA
Creatinine, µmol/L	24	81	180	68	22	32	174
Troponin[e], ng/L	125	4,607	654	545	10	340	1,793
BNP, ng/L	2,305	870	19,013	3,773	189	3140	>5,000
Treatment							
Tracheal intubation	No	No	Yes	Yes	No	No	Yes
Inotropes	Yes	No	Yes	Yes	No	Yes	Yes
IVIG doses	1	1	2	2	2	2	1
Corticosteroids	Yes	Yes	No	No	No	Yes	Yes
Outcome	Favourable	Favourable	Favourable	Favourable	Favourable	Favourable	Favourable

Note: ALT, alanine aminotransferase (ref <32 U/L); AST, aspartate aminotransferase (ref <32 U/L; BNP, brain-type natriuretic peptide (normal value <100 ng/L); COVID-19, coronavirus disease 2019; CT, computed tomography; IgG, immunoglobulin G antibodies; IVIG, intravenous immunoglobulins (2 g/kg intravenously); LDH, lactate dehydrogenase (ref 290–580 U/L).

Abbreviations: IVIG, intravenous immunoglobulin; KDSS, Kawasaki disease shock syndrome; MIS-C, multisystem inflammatory syndrome in children; NA, not available; ND, not done; Neg, negative; PICU, paediatric intensive care unit; PIMS-TS, paediatric multisystem inflammatory syndrome temporally associated with COVID-19; Pos, positive; RT-PCR, reverse transcription-polymerase chain reaction; WHO, World Health Organization.

[a]Close contact with patient with confirmed or highly suspected SARS-CoV-2.

[b]PCR on nasal swab for other respiratory viruses: adenovirus, bocavirus, coronavirus 229E, NL63 and OC43, enterovirus, influenza virus A H1 and H3, influenza virus B, metapneumovirus, parainfluenza virus 1, 2, 3 and 4, rhinovirus, respiratory syncytial virus A and B. *Do these all need to be listed?*

[c]Five major clinical criteria from American Heart Association.

[d]Highest value before diagnosis during hospital stay unless indicated otherwise.

[e]Troponin normal values: < 34 ng/ml.

TABLE 2 Description of close contacts with COVID-19 in seven children with MIS-C during the 2 months before the onset of their disease

Patient No.	Lockdown respected[a]	Contact with confirmed or suspected COVID-19			Symptoms between contact and MIS_C diagnosis	Day 1 Fever	Day 1 Hospital	Contact to COVID-19 (days)
		Yes/No	Day 1 of contact	Setting				
1	Yes	No	NA	NA	None	8 April	13 April	
2	Yes	Yes	7 March	Adult, party	None	13 April	19 April	37
3	Yes	No	NA	NA	None	14 April	19 April	
4	Yes	Yes	17 March	Grandfather, household	None	18 April	20 April	32
5	Yes	Yes	17 March	Mother[b], household	Cough, laryngitis on 1 April	15 April	20 April	34
6	Yes	Yes	30 March	Adult cousin, household	None	23 April	28 April	24
7	Yes	Yes	5 March	Father, household	None	30 April	5 May	58

Abbreviation: MIS-C, multisystem inflammatory syndrome in children.

[a]France's lockdown started on 17 march 2020.

[b]Child's mother continued to go to work and got COVID-19

MIS-C definition. All seven MIS-C patients were admitted to the PICU: the two boys stayed for 2 days and the five girls for three to 12 days. None of them had coronary aneurisms. An abnormal echocardiography was found in six of the seven MIS-C patients, mainly due to a low ejection fraction or mitral regurgitation. All seven children received intravenous immunoglobulins and four also received corticosteroids. The outcomes were favourable in all seven children (Table 1).

3.2 | Comparison of MIS-C patients and KD patients

From 1 January 2018 to 15 July 2020, we identified 40 children who presented with typical or atypical KD, including 10 who presented during the COVID-19 lockdown. None of them tested positive for SARS-Cov-2. We compared their patient demographics, clinical, laboratory, echocardiographic, therapeutic and outcomes with the seven children with MIS-C, who all tested positive for SARS-CoV-2 (Table 3). Compared to the children with KD, the children with MIS-C were older, and a lower proportion were under 5 years of age (14.3% vs. 85.0%, $p < 0.001$). The MIS-C patients were admitted to the PICU more frequently (100% vs. 10.0%, $p < 0.001$) and had higher frequencies of abdominal pain (71.4% vs. 12.5%, $p = 0.003$), myocardial dysfunction (85.7% vs. 5.0%, $p < 0.001$) and KD shock syndrome (85.7% vs. 2.5%, $p < 0.001$). The patients with MIC-C also had a higher mean +/− standard deviation of C-reactive protein (339 ± 131 vs. 153 ± 87, $p < 0.001$) and a lower mean +/− standard deviation of serum sodium (130 ± 4.2 vs. 134 ± 3.0, $p = 0.011$).

3.3 | Evolution of the MIS-C outbreak related to COVID-19 in France

Figure 1, panel B shows the evolution of the daily number of new cases of COVID-19 reported by the emergency departments sentinel surveillance network for the Paris region from March to July 2020, displayed by the week of occurrence. The period when French citizens were ordered to stay at home is included. The Figure also shows the MIS-C cases and the typical and atypical KD patients from March to July, displayed by the week of hospital admission. The first MIS-C cases occurred about 3 weeks after the peak of daily COVID-19 cases in the Paris region. None of the patients admitted after the second week of May had a SARS-CoV-2 infection or fulfilled the MIS-C criteria.

Figure 2 shows the correlation between the new weekly ED COVID-19 cases reported for the Paris region from March to July 2020 and the weekly number of children presenting with MIS-C and confirmed SARS-CoV-2 who were admitted to our hospital. For the correlation analysis, the weekly numbers of MIS-C cases were plotted against the new weekly ED COVID-19 cases for the region at four weekly time points before admission. Spearman's rho correlation coefficient for the same week that the children with MIS-C were admitted was 0.367 ($p = 0.102$). We also looked at the 1–4 weeks before admission and they were as follows: 0.465 ($p = 0.039$), 0.577 ($p = 0.01$), 0.705 ($p = 0.001$) and 0.724 ($p = 0.001$), respectively. The R-squared measures were highest (0.806) for the correlation between the weekly number of children with MIS-C and the weekly new ED COVID-19 cases reported in the Paris region 3 weeks before.

Figure S1 shows the COVID-19 pandemic evolution in France from March to July 2020. This includes the official cumulative

TABLE 3 Comparison between 40 typical or atypical Kawasaki disease patients and seven MIS-C patients with a SARS-CoV-2 infection

	Kawasaki disease (no SARS-CoV-2 infection) *N* = 40	MIS-C with SARS-CoV-2 infection *N* = 7	*p* value
Age, years	2.3 (2.0)	7.5 (4.0)	0.013
Age, younger than 5 years, *n* (%)	34 (85.0%)	1 (14.3%)	0.001
Sex, male, *n* (%)	26 (65.0%)	3 (42.9%)	0.403
PICU stay, *n* (%)	4 (10.0%)	7 (100.0%)	<0.001
Kawasaki major criteria[a]			
≥4, *n* (%)	17 (42.5%)	2 (28.6%)	0.685
Number of major criteria	3.2 (1.2)	2.9 (1.5)	0.503
Other symptoms			
Abdominal pain, *n* (%)	5 (12.5%)	5 (71.4%)	0.003
Aneurisms or dilated coronaries, *n* (%)	7 (17.5%)	0 (0.0%)	0.573
Ejection fraction[b] below 40%, *n* (%)	1 (2.5%)	4 (57.1%)	0.001
Mitral regurgitation, *n* (%)	10 (25.0%)	2 (28.6%)	1
Pericardial effusion, *n* (%)	11 (27.0%)	1 (14.3%)	0.659
Abnormal electrocardiography, *n* (%)	0 (0.0%)[e]	4 (57.1%)	0.001
Myocardial dysfunction, *n* (%)	2 (5.0%)	6 (85.7%)	<0.001
KDSS, *n* (%)	1 (2.5%)	6 (85.7%)	<0.001
Laboratory values[c]			
White blood cell count/µl	14,873 (4 583)	11,444 (7 903)	0.303
Neutrophil count/µl	9,572 (4 948)	9,783 (7,205)	0.925
Lymphocyte count/µl	3,790 (2,149)	866 (434)	<0.001
Haemoglobin, g/dl	10.0 (1.1)	9.1 (2.2)	0.322
Platelet count/µl	398,175 (170 885)	175,857 (69,247)	<0.001
CRP, mg/L	153 (87)	339 (131)	<0.001
CRP, >250 mg/L, *n* (%)	8 (20.0%)	6 (85.7%)	0.002
ALT, U/L	56 (67)	23 (16)	0.206
AST, U/L	53 (76)	55 (37)	0.951
Albumin (lowest), g/L	28.1 (4.5)	20.2 (2.2)	<0.001
Sodium (lowest), mEq/L	134 (3)	130 (4.2)	0.011
Sodium below 132 mEq/L, n (%)	8 (20.0%)	4 (57.1%)	0.06
Creatinine, µmol/L	23.2 (8.5)	83 (68.0)	0.059
Treatment			
Inotropic support, *n* (%)	1 (2.5%)	5 (71.4%)	<0.001
IVIG (number of doses)[d]	1.2 (0.4)	1.6 (0.5)	0.041
Corticosteroids, *n* (%)	7 (17.5%)	4 (57.1%)	0.042
Favourable outcome, *n* (%)	10 (100.0%)	7 (100.0%)	1

Note: Values are means (SD) unless indicated otherwise.

CRP, C-reactive protein; IVIG, Intravenous immunoglobulins; KDSS, Kawasaki disease shock syndrome; MIS-C, multisystem inflammatory syndrome in children.

[a]American Heart Association criteria.[19]

[b]Left ventricle ejection fraction.

[c]The highest value before diagnosis during hospital stay is reported unless indicated otherwise.

[d]All 47 patients received IVIG.

[e]Missing data on electrocardiography for 16 patients.

confirmed cases and new daily cases in France, as well as the 10 KD virus-negative cases and the MIS-C virus-positive cases during this period, displayed by when they were first seen in our hospital. We also plotted the weekly numbers of MIS-C cases against the new daily official COVID-19 cases for the whole of France at four weekly time points before those admissions (Figure S2). The results were

almost identical to those obtained for the COVID-19 cases in the Paris region.

4 | DISCUSSION

This study showed a strong lagged correlation between the rise and fall of the number of children and adolescents with MIS-C and the rise and fall of the first wave of the COVID-19 pandemic in France. To the best of our knowledge, this has not been reported before. The correlation was highest for the number of new COVID-19 cases reported 3–4 weeks before the occurrence of MIS-C cases. The correlations were similar when we used the number of new ED cases in the Paris region or the total number of new official cases for the whole of France. All seven of the MIS-C patients tested positive for SARS-CoV-2. Compared to children with KD, MIS-C patients were significantly older and were more likely to be admitted to the PICU. They also had a higher frequency of abdominal pain, myocardial dysfunction and KD shock syndrome, a higher C-reactive protein and lower serum sodium. During the period of the MIS-C outbreak, 10 children diagnosed with KD were admitted. They did not meet the MIS-C criteria and did not test positive for SARS-CoV-2.

To date, SARS-CoV-2 has not been definitely proved to cause MIS-C. However, MIS-C also appeared during outbreaks of COVID-19 in Europe[7–9] and the United States[13–16] and this link has been highly suggested.[22] The strong lagged correlation between the rise and fall of MIS-C cases, and the rise and fall of the first wave of the COVID-19 pandemic in France, reported in this paper further supports this association. If MIS-C is related to SARS-CoV-2, the delay between the peak of the virus in the general population and the MIS-C cases suggests a post-infectious phenomenon, rather than a condition resulting from an acute infection.[18] Our results are consistent with previous reports[7–9,16] of MIS-C cases. These have indicated an absence of COVID-19 symptoms before an MISC-C diagnosis, often negative RT-PCR results, very frequent positive antibodies, frequent family exposure and the development of MIS-C after a time lag of 3–6 weeks. These elements further suggest that SARS-CoV-2 may be acting as either a trigger or as an immune-modulating factor.[17] All seven of the MIS-C patients in our series tested positive for IgG antibodies, while only one tested positive for nasopharyngeal RT-PCR. It could be argued that the presence of antibodies to SARS-CoV-2 does not, in itself, imply a post-infectious process linked to MIS-C. This is because positive antibody tests could also become more and more common in children as the COVID-19 spreads in the population. However, this is not a likely explanation for the findings in our series. A cross-sectional prospective study conducted in the Paris region during approximately the same period as our study found that only 10.5% of 605 asymptomatic or pauci-symptomatic children aged 0–15 years tested positive for SARS-CoV-2 serology.[23] It is notable that 87.3% of those who tested positive in that study had confirmed or suspected COVID-19 contacts.[23]

We do not know the role played by lockdowns on the MIS-C outbreaks. It has been reported that many children are infected by their parents, so it is possible that these restrictions may have enhanced close contact and eventually increase the viral load from adults to susceptible children.

While MIS-C has been reported in several countries in Europe and in the United States, it has not been reported in China or Japan[22] where KD is more frequent. A series of KD patients in a paediatric Japanese hospital, published online in this journal in August 2020, found no increase in the incidence of KD or changes in its clinical features during the local COVID-19 pandemic.[24] It could be that MIS-C is such a rare condition that it has only been observed in countries with a very large number of COVID-19 cases, such as Italy, Spain, France, the UK and the United States.[22] The fact that the MIS-C cases in our report occurred during a shorter period than the first wave of the COVID-19 pandemic in France, and that the cases correlated with the peak of this pandemic, is consistent with this hypothesis. Figure S1 suggests that MIS-C cases appeared when the official number of new confirmed COVID-19 cases was around 4,500 per day in France. In reality, the real number of new cases would have been much higher, because the testing rate during the earlier stages of the pandemic was relatively low.

A clear and consensual definition of this new multisystem inflammatory syndrome that is temporally associated with COVID-19 is needed. The syndrome is currently referred to as PIMS-TS or just PIMS, MIS-C, multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19, Kawasaki-like disease or atypical KD. In our series, the use of the MIS-C, PIMS-TS and WHO definitions yielded the same results. Although this inflammatory condition shares multiple clinical and laboratory features with KD, some important differences exist.[17] Cheung et al[13] reported the clinical characteristics of 17 patients with PIMS: eight who met the criteria for typical KD and five for incomplete KD. Dufort et al[16] reported that 36% of the 99 MIS-C patients they studied also had a diagnosis of KD. The current case definition of MIS-C is very broad and would be met by children with many infectious and inflammatory conditions. In our series, only children who tested positive for SARS-CoV-2 fulfilled the MIS-C criteria. We suggest that an MIS-C diagnosis should only be given to children who test positive for SARS-CoV-2, as these infected patients have a clearly different clinical picture, as confirmed by Dufort et al.[16]

We did not collect racial or ethnic data, as this is not permitted in France. Previous case series have suggested that MIS-C primarily affects people of African or Caribbean ancestry.[8,9] However, one case series from New York reported that twelve out of seventeen patients they studied were white.[13] Although predisposing genetic factors have been described for KD, caution is necessary when interpreting the current racial or ethnic data for MIS-C. An alternative explanation may be that there is a higher prevalence of SARS-CoV-2 in some groups, with the spread of infection driven by decreased opportunities for social distancing because of dense housing. Some groups with a higher prevalence of SARS-CoV-2 are also more likely to be essential key workers or have to work for economic reasons.[25] Social disparities have been reported for COVID-19.

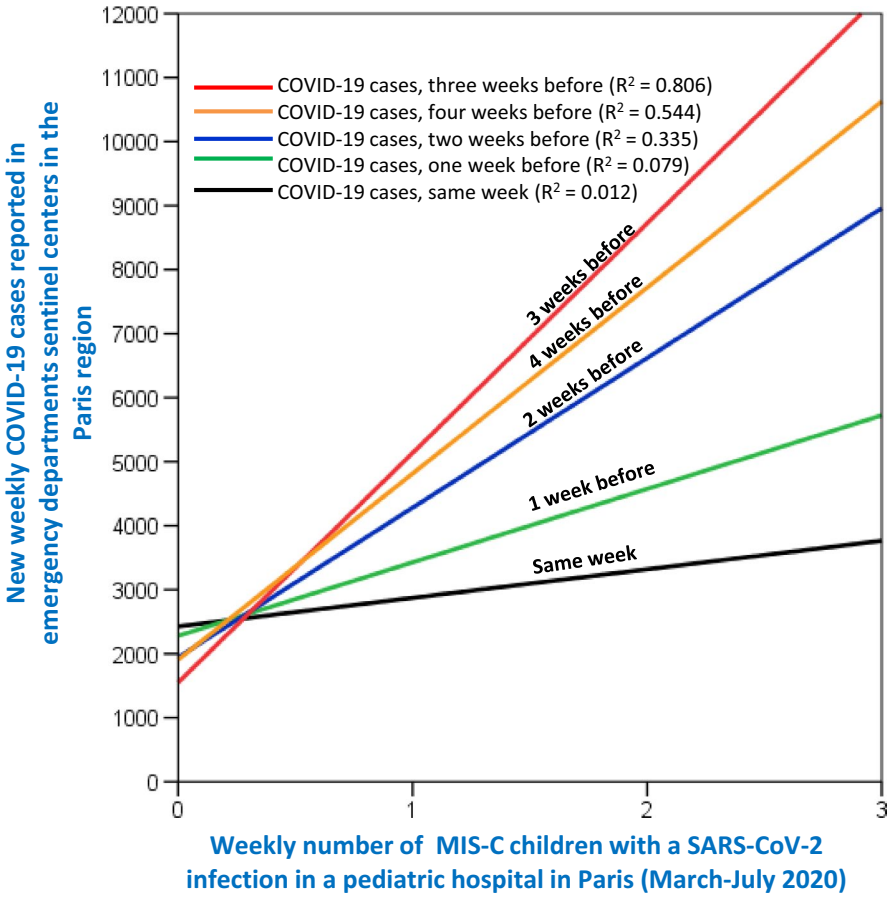

FIGURE 2 Correlation between new weekly COVID-19 cases reported for the Paris region from March to July 2020 and weekly number of children presenting with MIS-C and SARS-CoV-2 to our paediatric university hospital. The figure shows correlations between the weekly number of MIS-C cases and weekly COVID-19 cases that were reported in the region during the same week (black regression line, Rho 0.367, p = 0.102), 1 week before (green, Rho 0.465, p = 0.039), 2 weeks before (blue, Rho 0.577, p = 0.01), 3 weeks before (red, Rho 0.705, p = 0.001) and 4 weeks before (orange, Rho 0.724, p = 0.001). The R-squared measure was highest for the correlation between the weekly MIS-C and weekly new COVID-19 cases reported 3 weeks before. Rho, Spearman's rho correlation coefficient

This study had some limitations. Its retrospective design meant that there were less data on inflammatory investigations in the 30 children with KD admitted during the pre-COVID-19 pandemic, which precluded a larger comparison with MIS-C patients. Second, this was a single-centre study with few patients and the results may have been due to local variations. Third, the data on the MIS-C outbreak were only collected for 3 months, with a short follow-up period. However, the decline of the observed outbreak was as sharp as its rise and no new cases of MIS-C were seen during the last 2 months of the study period. Fourth, although the correlation between the rise and fall of the MIS-C outbreak and the COVID-19 pandemic was very strong, it does not provide formal proof of causality. Fifth, correlations should be interpreted with caution because of the small sample size.

5 | CONCLUSION

The rise and fall of the COVID-19 epidemic were associated with the rise and fall of an outbreak of MIS-C in children and adolescents in France. The fall in the MIS-C cases as the first wave of the COVID-19 pandemic reduced in intensity in France further supports their association. Although MIS-C has been relatively rare, clinicians should be aware of this new clinical presentation, as more cases are likely if the second wave of COVID-19 epidemic has the same impact as the first one. Because the number of patients by MIS-C is relatively low, it is very important to carry out multicentre studies, so that we can develop a better understanding of this new condition.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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