Multisystem Inflammatory Syndrome in Children

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Researchers report nearly 300 cases of inflammatory syndrome tied to Covid-19 in kids

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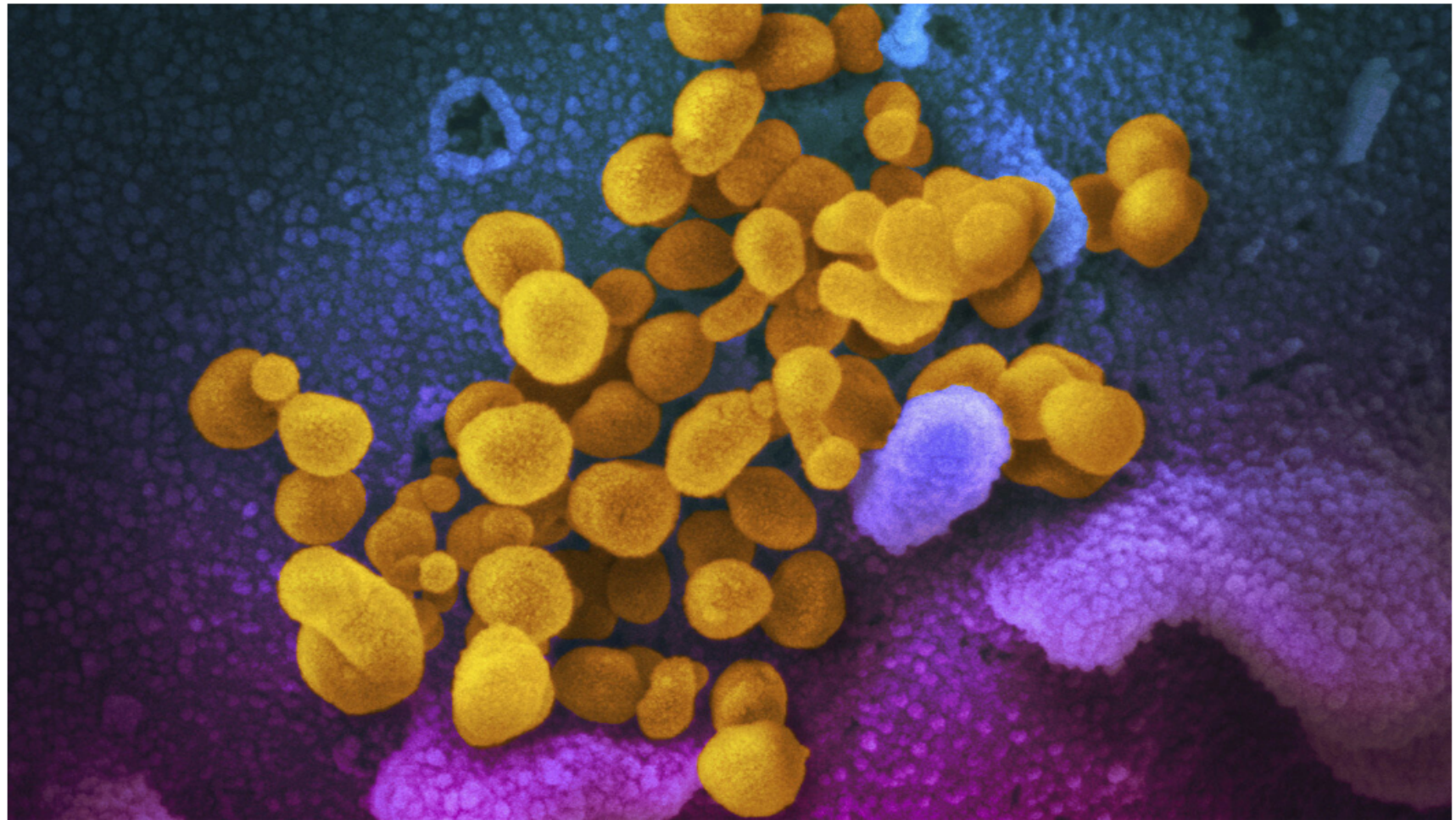
Reprints



Game plan for today

- Background on MIS-C (in US and other countries that have reported on this disorder)
- Reminder about Kawasaki Disease
- Review of several case series on MIS-C in US, Italy, UK
- Highlights of clinical findings
- Areas for future research

Objectives

- Recognize that severe post-COVID infection outcomes can occur in young patients aged 1 to 21 years of age..despite their not being very sick with COVID
- Recite clinical features of MIS-C
- List types of treatment strategies that you could use if faced with clinical management of MIS-C cases
- Recognize your role in reporting MIS-C to CDC

Take home messages

- MIS-C is a rare but serious outcome of COVID-19 infection in children and adolescents
- Hypothesized to be a consequence of immune-mediated injury triggered by COVID infection
- Symptoms and signs are similar to Kawasaki Disease
- Age range appears broader than KD
- Few epi or clinical studies reported to date—mostly case series that summarize clinical test results
- Unknown at present if this condition will be a significant concern in Indian country
- We currently have more questions than answers about MIS-C

Background

On April 26, 2020, clinicians in the United Kingdom (UK) recognized increased reports o
healthy children presenting with a severe inflammatory syndrome with Kawasaki disea
features.[1] The cases occurred in children testing positive for current or recent infection
2, the novel coronavirus that causes COVID-19, based on reverse-transcriptase polymer
reaction (RT-PCR) or serologic assay, or who had an epidemiologic link to a COVID-19 ca
presented with a persistent fever and a constellation of symptoms including hypotensi
(e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic) involve
elevated inflammatory markers.[2] Respiratory symptoms were not present in all cases.

Kawasaki disease

Kawasaki disease is an acute and usually self-limiting vasculitis the medium calibre vessels, which almost exclusively affects children.[12, 13] In the acute phase of the disease, patients with Kawasaki disease might have haemodynamic instability, a cond known as Kawasaki disease shock syndrome (KDSS).[14] Other patients with Kawasaki disease might fulfil the criteria of macrophage activation syndrome (MAS), resembling secondary haemophagocytic lymphohistiocytosis.[15] The cause of Kawasak disease remains unknown; however, earlier evidence[16] suggests an infectious agent triggers a cascade that causes the illness.

Kawasaki Disease

- Fever/temp elevation
- Erythroderma
- Delayed desquamation
- Multi-organ involvement
- Coronary artery aneurism common
- Likely post-viral
- Abnormal cardiac echos are common…follow up includes repeated echos

Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
[ii]Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Italian study, Lancet, June 6, 2020

- Outbreak of Kawasaki-like disease in Bergamo
- Case series of 10 cases during early pandemic, compared to 19 in pre-pandemic at one hospital
- Chart review of clinical and lab data pre- and post- pandemic
- Appropriate case definition
- Simple analysis—comparisons of means, mostly
- Conclusions: little difference in presentations, clinical findings, lab findings between groups. Big difference in freq of disease occurrence
- Rx: immunoglobulin, aspirin, steroids.

NY and Boston case series

The nearly 300 cases identified in these two studies share some similarities wit
but there are also differences. Few of the children are under the age of 5. The a
age of children in the larger study was 8; 42% of the children in the New York
were aged 6 to 12.

Another difference: While KD disproportionately affects children of Asian des
MIS-C cases in the New York cohort were of all racial and ethnic backgrounds
researchers reported.

"Among our patients, predominantly from the New York Metropolitan Region
were Black and 36% were Hispanic. This may be a reflection of the well-docun
elevated incidence of SARS CoV-2 infection among black and Hispanic
communities," they wrote.

The New York group estimated that the majority of MIS-C cases occurred abo
month after the peak of Covid-19 cases in the state. They estimated that betwe
March 1 and May 10, two of every 100,000 people under the 21 years of age wh
laboratory-confirmed SARS-CoV-2 virus developed MIS-C in the state. The in
rate in people under the age of 21 years was 322 in 100,000 over that period.

NY State MIS-C surveillance report in NEJM (Dufort et al)

- 99 cases reported, 30% aged 0-5 years, in 126 hospitals
- Common clinical presentation: fever, chills; tachycardia; GI; rash; conjunctival injection; mucosal changes
- Lab: increased inflammatory markers 100%
- Work up: 59% had myocarditis, 80% ICU, 2% mortality
- One-third of patients had pre-existing condition
- Key findings: clinical presentation varied by age group

NY State MIS-C surveillance, cntd

- Higher proportion of dermatologic manifestations in youngest patients
- Myocarditis more common in adolescents
- All racial groups in the case series, somewhat different than with KD

- Limitations due mostly to incomplete case ascertainment

Multistate case series, in NEJM June 26, 2020 (Feldstein et al)

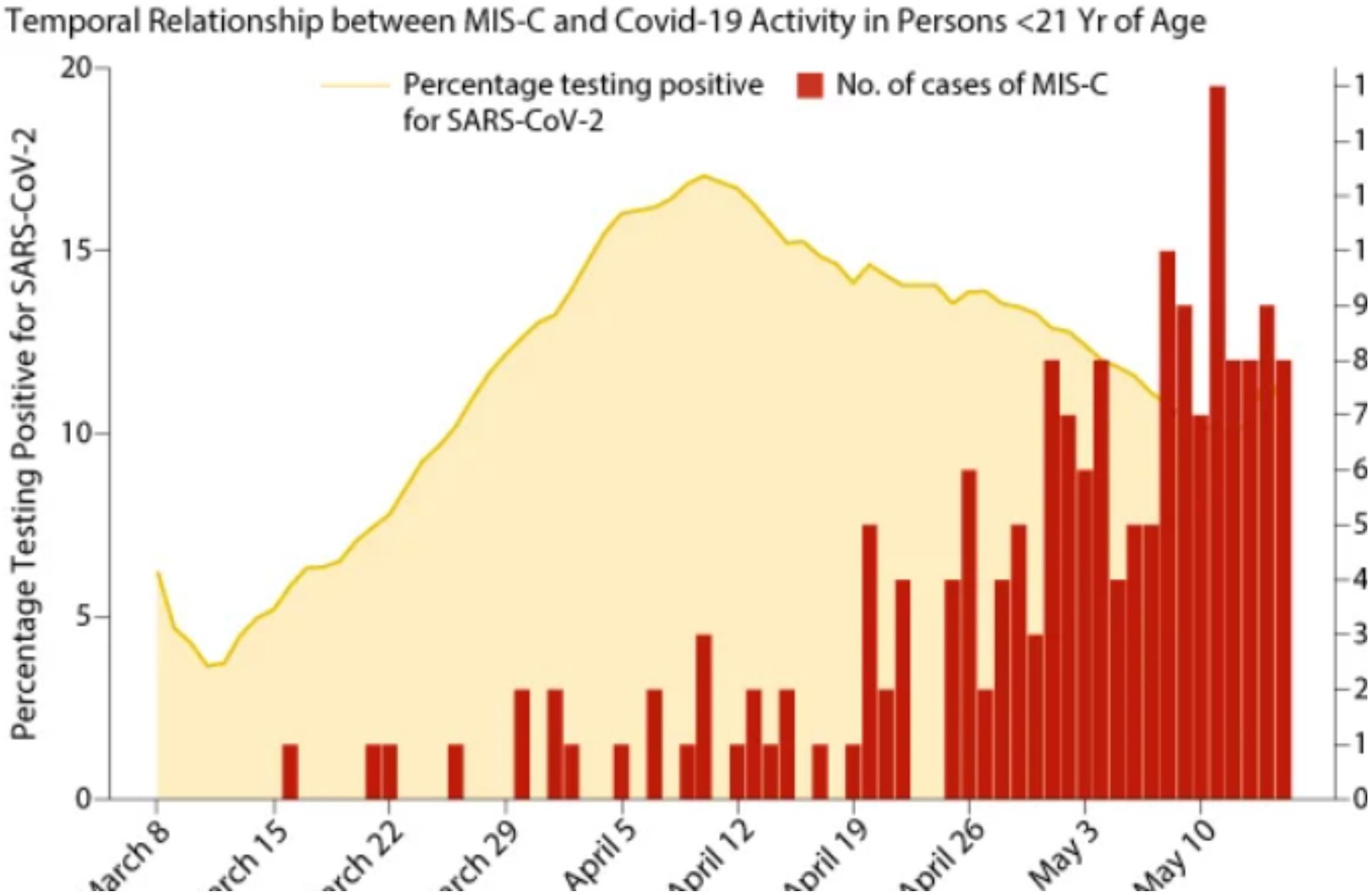
- 186 cases of MIS-C in 26 states, part of a COVID infection surveillance program at 31 sites
- Median age of cases: 8.3 years
- Common organ system involvement :GI, CV, heme, respiratory >70%
- Four organ systems involved in ¾ th of cases
- Common therapies: immunoglobulin, glucocorticoids, IL-6, 1RA inhibitors
- 80% icu, 20% intubated, 2% died
- KD-like features in 40%

- Unlike KD that presents with cv shock among 5% of the cases, this series had cv shock in 50%

Table 2. Clinical Characteristics of the Patients According to the Number of Kawasaki's Disease–like Features Present.*

Characteristic	Patients with 4 or 5 Features (N=38)	Patients with 2 or 3 Features plus Laboratory Findings (N=36)	Other (N=112)†	All Patients (N=186)
Median age (IQR) — yr	5.7 (1.7–8.9)	8.4 (4.2–12.0)	9.1 (3.1–14.1)	8.3 (3.3–12.5)
Signs and symptoms				
Fever‡	38 (100)	36 (100)	112 (100)	186 (100)
Median fever duration (IQR) — days	6 (6–8)	6 (6–8)	6 (4–8)	6 (5–8)
Fever duration — no./total no. (%)				
≤3 days	0	0	16/93 (17)	16/167 (10)
4 days	0	0	20/93 (22)	20/167 (12)
≥5 days	38/38 (100)	36/36 (100)	57/93 (61)	131/167 (78)
Bilateral conjunctival injection — no. (%)	36 (95)	30 (83)	37 (33)	103 (55)
Oral mucosal changes — no. (%)	38 (100)	16 (44)	24 (21)	78 (42)
Peripheral extremity changes — no. (%)	36 (95)	14 (39)	19 (17)	69 (37)
Rash — no. (%)	38 (100)	27 (75)	45 (40)	110 (59)
Cervical lymphadenopathy >1.5 cm diameter — no. (%)§	7 (18)	3 (8)	8 (7)	18 (10)
Echocardiography performed — no. (%)	37 (97)	35 (97)	98 (88)	170 (91)
LAD or RCA z score of ≥2.5¶	3 (8)	8 (23)	4 (4)	15 (9)
Treatment				

Treatment				
Intravenous immune globulin — no. (%)	38 (100)	35 (97)	71 (63)	144 (77)
Median day of illness on which treatment was received (IQR)	6 (6–8)	7 (6–8)	6 (5–8)	6 (5–8)
Second dose received — no. (%)	16 (42)	9 (25)	14 (12)	39 (21)
Systemic glucocorticoid — no. (%)	20 (53)	18 (50)	53 (47)	91 (49)
Interleukin-6 inhibitor — no. (%)‖	1 (3)	1 (3)	12 (11)	14 (8)
Interleukin-1Ra inhibitor — no. (%)**	5 (13)	6 (17)	13 (12)	24 (13)
Anticoagulation therapy — no. (%)††	14 (37)	18 (50)	55 (49)	87 (47)
Highest level of care				
Ward — no. (%)	13 (34)	2 (6)	23 (21)	38 (20)
Intensive care unit — no. (%)	25 (66)	34 (94)	89 (79)	148 (80)


Temporal Relationship between MIS-C and Covid-19 Activity in Persons <21 Yr of Age
Percentage testing positive for SARS-CoV-2
No. of cases of MIS-C
Percentage Testing Positive for SARS-CoV-2
20
15
10
5
0
1
1
1
1
9
8
7
6
5
4
3
2
1
0
March 8
rch 15
rch 22
rch 29
April 5
April 12
April 19
April 26
May 3
May 10

Limitations: multi-state case series of MIS-C

- Generalizability limited
- Timing of infection unknown
- Duration of illness was not well-documented in all cases
- Some NY cases were excluded that had been earlier reported in other reports

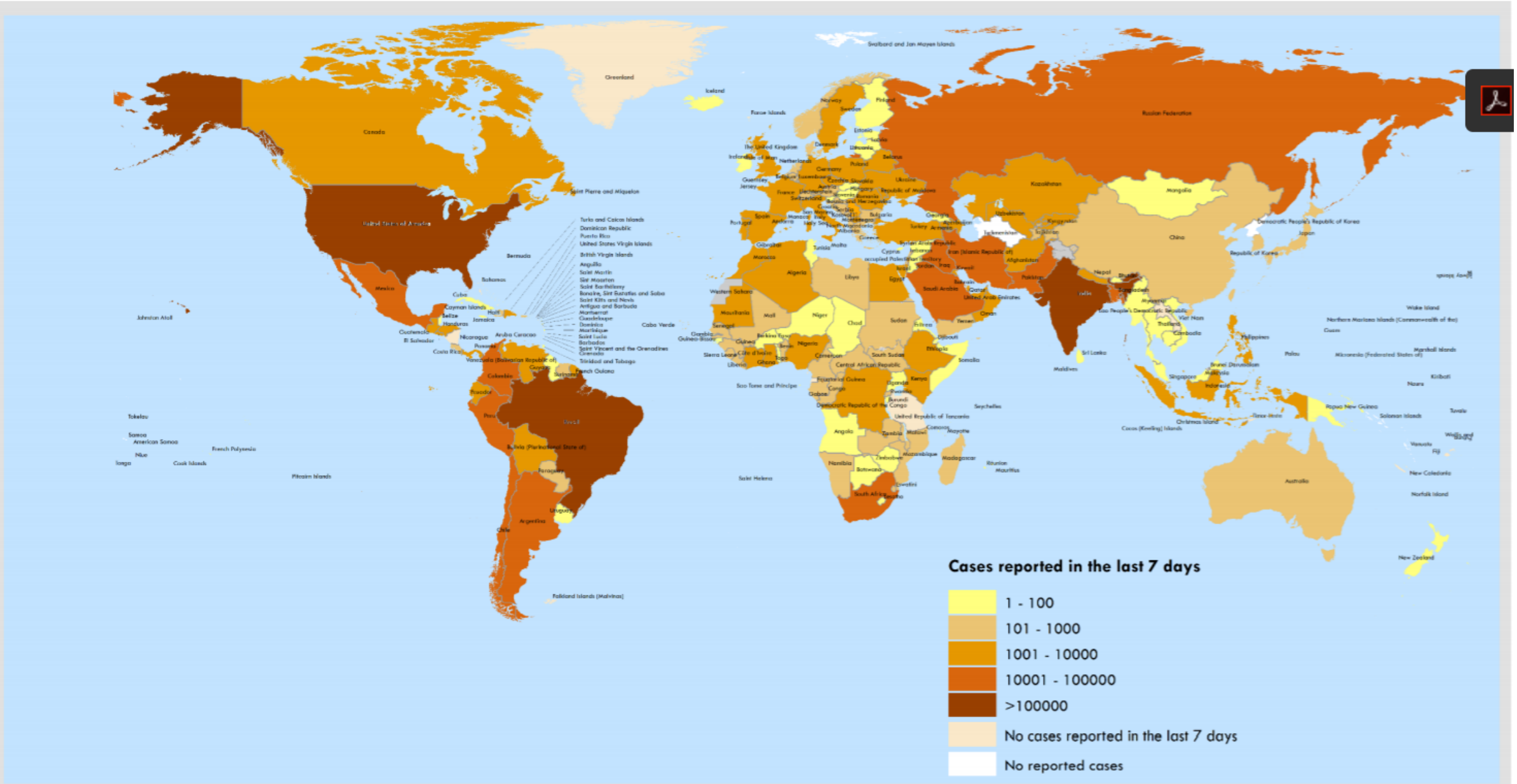
Research and other needs:

- Appropriately-designed cohort studies, tho expensive and outcome may be rare
- Better identification of risk factors leading to disease using a case-control study approach (cases with MIS-C, age-matched controls without MIS-C but with h/o documented COVID infection)
- Long-term outcomes post MIS-C in children
- Pathogenesis
- Determine if similar outcome in adults
- Improved management strategies (RCT's?)
- Education of clinicians and parents about this potential outcome of infection

Links to articles in NEJM

- https://www.nejm.org/doi/full/10.1056/NEJMoa2021680
- https://www.nejm.org/doi/full/10.1056/NEJMoa2021756

Figure 1. Number of confirmed COVID-19 cases reported in the last seven days by country, territory or area, 24 June to 30 June**



***Data Source**: World Health Organization*
***Map Production**: WHO Health Emergencies Programme*

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