Epidemiology of Exposures, Preceding Illness and Testing History in Children With Multisystem Inflammatory Syndrome in Children in the First 18 Months of the COVID-19 Pandemic, Los Angeles County, California

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M ultisystem Inflammatory Syndrome in Children (MIS-C) was first identified in Europe and the United States in April 2020 following the first Coronavirus Disease-2019 (COVID-19) waves.1 It has been established as a rare, but severe complication of COVID-19, and its clinical presentation has been well described.1,2 As of October 4, 2021, 5217 cases of confirmed MIS-C had been reported to the US Centers for Disease Control and Prevention (CDC).3 Population-level data and case studies describe the temporal association of MIS-C to COVID-19, with increases in MIS-C following COVID-19 surges by 2–6 weeks.1,4 From March 2020 to September 2021, a similar trend was noted among Los Angeles County (LAC) residents <21 years old, with acute severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections peaking the week ending January 9, 2021, and reported MIS-C cases peaking 3 weeks later during the week ending January 30, 2021. In this study, we build upon the epidemiological link between COVID-19 and MIS-C by describing the history of COVID-19 exposure, preceding illness, and SARS-CoV-2 testing in a large group of children with MIS-C in LAC from March 2020 to September 2021. With Food and Drug Administration emergency use authorization of COVID-19 vaccination for children ages 5–11 years5 and widespread pediatric infection during Omicron variant surges,6 improving our understanding of the epidemiology and exposure history of those with MIS-C will help inform future surveillance.

MATERIALS AND METHODS

Our descriptive study included all confirmed cases of MIS-C with symptom onset between March 1, 2020, and September 30, 2021 identified by the LAC Department of Public Health, using the CDC case definition.7 Charts were reviewed for documentation of (1) prior SARS-CoV-2 exposure, (2) preceding COVID-19-like illness, and (3) SARS-CoV-2 testing history. Cases were reviewed for alternate diagnosis and those with documentation of a confirmed alternate diagnosis were excluded. Per CDC guidance, some individuals met criteria for Typical or Atypical Kawasaki Disease (KD), but were included if they met criteria for MIS-C. Study activities were approved by the LAC Department of Public Health Institutional Review Board. A waiver of consent was obtained for this study.

Self-reported exposure status was defined as (1) confirmed if there was a known exposure to a clinically diagnosed or laboratory-confirmed COVID-19 case; (2) suspected if there was a known or suspected exposure to an individual with symptoms concerning for COVID-19 but no clinical or laboratory diagnosis; (3) no known exposure if the family denied exposure to known cases of COVID-19; or (4) unknown if information was not available. Exposure timing was calculated from time of exposure to onset of MIS-C symptoms and recorded as an ordinal, noncontinuous variable rounded down to the nearest 2-week interval. When available, exposure setting was categorized as (1) household, (2) nonhousehold (excluding school and day care), (3) school or day care, or (4) unspecified if exposure setting was not documented. Parents and siblings were assumed to live in the same household, and friends and extended family were assumed to be nonhousehold, unless otherwise documented.

We defined “preceding illness” as symptoms concerning for COVID-19 regardless of laboratory testing occurring at any time before the MIS-C illness (fever/chills, myalgia/arthralgia, fatigue/malaise, cough, etc.). Laboratory testing for SARS-CoV-2 during MIS-C admission included reverse-transcriptase polymerase chain reaction (RT-PCR) and serological testing for SARS-CoV-2 IgG (qualitative and quantitative). Positive RT-PCR or serology testing during MIS-C admission was interpreted as evidence of prior SARS-CoV-2 infection. Prior history of COVID-19 testing was defined as self-reported positive laboratory or at-home SARS-CoV-2 testing (ie, PCR, antigen or not-specified) before MIS-C illness onset. Documentation of the specific assay used for SARS-CoV-2 testing was usually unavailable. Descriptive analysis was performed using SAS (9.4).

RESULTS

A total of 244 confirmed MIS-C cases were identified during the study period. Table 1 describes the cases’ exposure histories, preceding illness, and SARS-CoV-2 testing. Only 23 MIS-C cases (9.4%) had an unknown exposure history. The majority (61.9%)...
TABLE 1. Demographics and Epidemiology of Preceding SARS-CoV-2 Exposure, Illness and Testing History* of MIS-C in LAC

| Race/Ethnicity (n = 244) | n (%) |
|--------------------------|-------|
| Hispanic/LatinX          | 170 (69.7) |
| Black (non-Hispanic)     | 33 (13.5) |
| White (non-Hispanic)     | 25 (10.2) |
| Asian, Pacific Islander, Native Hawaiian (non-Hispanic) | 7 (2.9) |
| Other/unknown (non-Hispanic) | 9 (3.7) |

| Age (n = 244), years | n (%) |
|---------------------|-------|
| 0–5                 | 84 (34.4) |
| 6–10                | 71 (29.1) |
| 11–15               | 63 (25.8) |
| 16–20               | 26 (10.7) |
| Median age in years, Range | 9.0 (0.3-19.8) |

| Sex (n = 244) | n (%) |
|---------------|-------|
| Female        | 96 (39.3) |
| Male          | 148 (60.7) |

| SARS-CoV-2 testing during MIS-C admission | n (%) |
|-------------------------------------------|-------|
| RT-PCR (n = 243)                          | 78 (32.1) |
| Serology (n = 237)                        | 232 (97.9) |

| Preceding SARS-CoV-2 Exposure (n = 244) | n (%) |
|---------------------------------------|-------|
| Confirmed                              | 148 (60.7) |
| Suspected                              | 11 (4.5) |
| No known exposure                      | 62 (25.4) |
| Unknown                                | 23 (9.4) |

| Exposure setting (n = 159) | n (%) |
|---------------------------|-------|
| Household†                | 133 (83.6) |
| Nonhousehold‡             | 44 (28.1) |
| Multiple exposures§       | 5 (5.0) |
| School or day care        | < 5 (**) |
| Unspecified               | < 5 (**) |

| Exposure timing (n = 152), weeks | n (%) |
|----------------------------------|-------|
| <4                               | 14 (9.2) |
| 4–<6                             | 63 (41.5) |
| 6–<8                             | 55 (36.2) |
| 8–<12                            | 9 (5.9) |
| ≥12                              | 11 (7.2) |
| Weeks to exposure, range         | 1-32 |

| Evidence of preceding SARS-CoV-2 infection* (n = 244) | n (%) |
|------------------------------------------------------|-------|
| Symptomatic preceding COVID-19-like illness          | 89 (36.5) |
| Preceding positive SARS-CoV-2 test*                 | 80 (32.8) |
| Either preceding positive test* or preceding illness or confirmed/suspected exposure | 185 (75.8) |
| No preceding positive test* or preceding illness or confirmed/suspected exposure | 59 (24.2) |

| Timing of preceding illness or prior positive SARS-CoV-2 Test* (n = 120), weeks | n (%) |
|---------------------------------------------------------------------------|-------|
| <4                          | 18 (15.0) |
| 4–<6                        | 52 (43.3) |
| 6–<8                        | 38 (31.7) |
| 8–<12                       | 6 (5.0) |
| ≥12                         | 6 (5.0) |
| Weeks to preceding illness or prior positive test, range**             | 0–23.7 |

*"Testing" and "test" includes any reported positive test for acute SARS-CoV-2 infection before onset of MIS-C illness, that is, PCR, antigen and nonspecified. This does not include SARS-CoV-2 IgG or IgM antibody (serology) testing.
†Includes parents, siblings and any other family reported to reside in household with case.
‡Includes grandparents, friends and extended family, excluding school or day care exposure.
§Includes any case with more than 1 reported exposure.
¶Case counts <5 suppressed to protect the identity of patients.
*Includes cases with no specified exposure setting.
**Eighty-seven cases had a date recorded for onset of preceding illness or prior positive test.

had a confirmed exposure. The most common social setting exposure was household exposure (81.5%). Fewer than 5 cases reported an exposure in a school or day care setting. Exposure timing was available for 155 cases (63.5%). The majority of those with known exposure timing reported exposures 4–8 weeks (76.2%) before MIS-C onset (range 1–32 weeks). Ten cases (6.5%) reported exposure >12 weeks before MIS-C onset.

Over half of all cases (51.2%) had either preceding illness or preceding positive SARS-CoV-2 test, but only 18% reported both preceding illness and preceding positive test (Figure 1). For cases with date of preceding illness or preceding positive test available, the median time from preceding illness or preceding positive test to MIS-C onset was 4.7 weeks (mean 5.1, range 0–23.7 weeks, interquartile range 2.9 weeks). Three-quarters of all cases (75.8%) had either preceding illness or preceding positive SARS-CoV-2 test or known/suspected exposure to COVID-19. The remaining 59 cases (24.2%) were linked to COVID-19 through positive RT-PCR or serology during MIS-C admission. RT-PCR testing was positive in 78 (32.1%) of the 243 cases tested during their MIS-C hospitalization. Admission serologic testing for SARS-CoV-2 IgG was performed for 237 cases (97.1%) and was overwhelmingly positive (97.9%).

DISCUSSION

We describe in detail our cases’ history of COVID-19 exposure, preceding illness, and SARS-CoV-2 testing. We found that most confirmed and suspected exposures occurred 4–8 weeks before MIS-C symptom onset, although the range of 1–32 weeks suggests that there may be MIS-C cases occurring outside of this typically quoted time period. Additionally, the majority of documented exposures occurred in the home. Our findings support the use of serological testing for cases of suspected MIS-C with no known exposure or prior infection.

Population-level data describes MIS-C to be temporally associated with COVID-19, following patterns of COVID-19 cases in the general population by 2–6 weeks.1 Our study found that most cases with confirmed or suspected exposure had an exposure to COVID-19 4–8 weeks before MIS-C onset. A similar majority of cases had evidence of prior infection with either a preceding positive test or symptoms of COVID-19 4–8 weeks before MIS-C onset. Although the current MIS-C case definition requires positive COVID-19 testing results or exposure to a COVID-19 case within the 4 weeks before the symptom onset, over 75% of our cases had exposures greater than 4 weeks prior. MIS-C may still need to be considered in children with exposures more than 4 weeks before their presentation with MIS-C, especially in those who otherwise do not meet PCR or serologic testing criteria.

Our finding that most known or suspected exposures occurred in the home should be interpreted with caution given the extent of school closures in LAC during the study period. On March 16, 2020, the largest school district in LAC, Los Angeles Unified School District closed to reduce transmission of COVID-19. 8 Los Angeles Unified School District fully reopened for in-person learning August 16, 2021.16 However, other studies conducted with open schools have also found that the majority of COVID-19 exposures among MIS-C cases occurred in the home,18 so it is possible that our findings may hold true even after school reopening.

In our study, most confirmed MIS-C cases had positive serology, suggesting that serology is useful in establishing COVID-19 linkage in suspected cases, especially when prior infections and exposures are unknown. However, the utility of serological testing is changing as more children are vaccinated or demonstrate immunity via natural infection, making information regarding timing of exposure and prior infection critically important. Further research is needed regarding the persistence of seropositivity in children, the role of nucleocapsid (natural immunity) versus spike protein antibodies (natural or vaccine immunity) in the pathophysiology of MIS-C, and the role and utility of quantitative serology in the diagnosis of MIS-C.
FIGURE 1. Overlap in epidemiologic link to SARS-CoV-2 in reported MIS-C cases.

Approximately one-third of our study population reported preceding COVID-19-like illness. Two large cohort studies of MIS-C found similar proportions of patients with preceding illness.1,2 As such, it is prudent for clinicians caring for COVID-19 infected children to give anticipatory guidance for MIS-C and instructions for return precautions if symptoms develop weeks to months later.

Compared with a large MIS-C cohort study by Dufort et al., our study population had a higher proportion of cases with exposure to a confirmed case of COVID-19 (60.7% vs 38%). Only 1 patient (1%) in Dufort’s cohort had positive SARS-CoV-2 testing for preceding illness, whereas 80 cases in our study (32.8%) had preceding positive SARS-CoV-2 testing. These differences likely reflect the larger size of our study population as well as the expansion of testing compared with early in the pandemic.

Our study has several limitations. MIS-C is a reportable condition.11 However, despite outreach to healthcare providers, cases are likely underreported. We were also limited to documentation found in the hospital records, and history of exposure and symptoms as recalled by the cases’ caregivers. Additionally, because of limited documentation of work-up for alternate diagnoses and overlap in clinical characteristics between KD and MIS-C, some patient presentations may have been misattributed to MIS-C. More research is needed to understand if KD and MIS-C are unique pathological processes. Finally, as we present a study with a large, diverse population, the findings here may not be generalizable to other locations.

We provide detailed evidence regarding COVID-19 exposures and preceding illness before onset of MIS-C. Although most studies show COVID-19 exposures occurring in the preceding 2–6 weeks,1 the majority of our study population’s exposures occurred 4–8 weeks before MIS-C onset. Providers should obtain details for any history of COVID-19-like illness and exposures for patients with MIS-C. Additionally, our findings suggest that the use of serology can help establish epidemiological links to COVID-19 when past infection or exposure are unknown. These findings have important implications for future surveillance for this rare and serious sequela of COVID-19.

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