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NATIONAL CENTER FOR IMMUNIZATION & RESPIRATORY DISEASES

# Risk Factors Associated with Multisystem Inflammatory Syndrome in Children: A Case Control Investigation

**Laura D. Zambrano, PhD, MPH[1]; Michael J. Wu, MSc[1]; Lora Martin, MSN[2]; Lacy Malloch, BS[2]; Sabrina Chen, BS[3]; Margaret Newhams, MPH[3]; Suden Kucukak, MD[3]; Mary Beth Son, MD[3,4]; Cameron Sanders, BS[2]; Kayla Patterson, MSc[2]; Natasha Halasa, MD[5]; Janet Chou, MD[3,4]; Manish M. Patel, MD, MS[1]; Adrienne G. Randolph, MD, MSc[3,4,6]; Angela P. Campbell, MD, MPH[1]; Charlotte V. Hobbs, MD[2]; for the *Overcoming COVID-19* investigators**

1. COVID-19 Response Team, Centers for Disease Control and Prevention, Atlanta, GA; 2. University of Mississippi Medical Center, Jackson, MS; 3. Boston Children's Hospital, Boston, MA; 4. Department of Pediatrics, Harvard Medical School, Boston, MA; 5. Division of Pediatric Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN; 6. Department of Anaesthesia, Harvard Medical School, Boston, MA

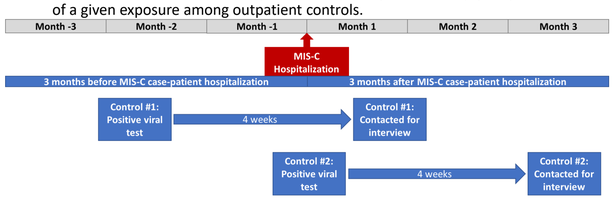
## BACKGROUND

- Risk factors underlying multisystem inflammatory syndrome in children (MIS-C), a hyperinflammatory condition associated with prior SARS-CoV-2 infection,[1] remain unclear.
- Race/ethnicity and social vulnerability have been previously linked to MIS-C.[2]
- MIS-C also shares pathophysiology with classic autoimmune and rheumatologic diseases.[3]
- MIS-C development after infection may be associated with:
  - Specific community and household exposures.
  - Host susceptibility to immune dysregulation after infection and the degree and timing of antigenic exposure.[4]

**Objective:** Examine potential risk factors by comparing MIS-C patients and SARS-CoV-2 positive outpatients at risk for MIS-C.

## METHODS

- Inclusion criteria:
  - MIS-C patients were hospitalized in 2021 across 14 US pediatric hospitals.
  - Outpatient non-MIS-C controls tested positive for SARS-CoV-2 within 3 months of their respective case-patient admission date and were frequency-matched by age group (0–4 years, 5–11 years, 12–15 years, 16–20 years) and site.
- Telephone surveys with caregivers queried exposures one month prior to MIS-C (cases) or one month after infection (controls).
- Associations between potential risk factors and MIS-C were assessed through mixed effects multivariable logistic regression.
- Population-attributable risk (PAR) was estimated for all exposures significantly associated with MIS-C as: PAR= pe × (OR − 1)/(1 + pe × [OR − 1]); pe = prevalence of a given exposure among outpatient controls.




## RESULTS

- Among 275 case-patients and 496 controls, MIS-C was associated with:
  - Large event attendance (≥10 people)
  - School attendance with limited mask-wearing
  - Public transit
  - Household crowding
  - Having a household member test positive for SARS-CoV-2.
- These exposures collectively accounted for ~51% of PAR for MIS-C.
- Controls were more likely to have reported >1 positive SARS-CoV-2 test at least 1 month apart.
- Race/ethnicity, social vulnerability, underlying medical conditions, and family history of autoimmune or rheumatologic disease were not associated with MIS-C.

## CONCLUSIONS

Factors potentially reflective of repeated or high viral exposures in the month after SARS-CoV-2 infection were each independently associated with developing MIS-C after infection. This investigation clarifies exposure profiles associated with MIS-C, reinforces the importance of non-pharmaceutical interventions to prevent viral exposure, and may inform future studies on the pathophysiology of MIS-C.

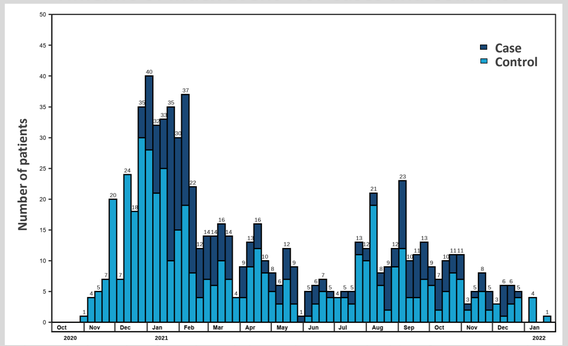
# High or frequent viral exposures may promote MIS-C development after SARS-CoV-2 infection.

***Overcoming COVID-19* group authors**: Julie C. Fitzgerald, MD (Children's Hospital of Philadelphia); Matthew K. Leroue, MD (Children's Hospital Colorado); Mark Hall, MD (Nationwide Children's); Katherine Irby (Arkansas Children's), MD; Courtney M. Rowan, MD, MSc (Riley Hospital for Children); Kari Wellnitz, MD (Stead Family Hospital); Leila C. Sahni, PhD, MPH (Texas Children's); Laura Loftis, MD (Texas Children's); Tamara T. Bradford, MD (Children's Hospital of New Orleans); Mary Staat, MD (Cincinatti Children's); Christopher Babbitt, MD (Miller Children's and Women's Hospital); Christopher L. Carroll, MD (Connecticut Children's); Pia S. Pannaraj, MD (Children's Hospital Los Angeles); Michele Kong, MD (Children's of Alabama); Jennifer E. Schuster, MD (Children's Mercy Kansas City)

**References**

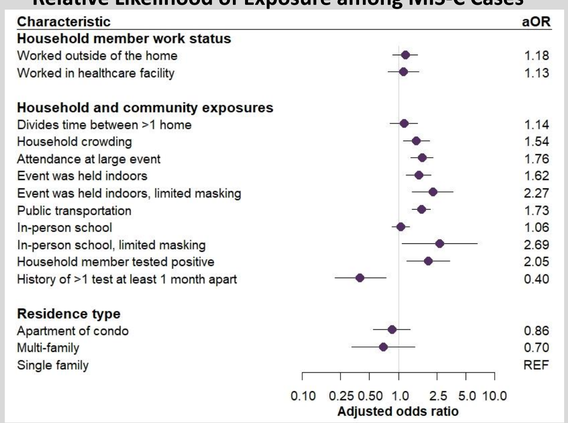
1. Feldstein LR et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med*. Jul 23 2020; doi:10.1056/NEJMoa2021680
2. Zambrano LD et al.. Investigating Health Disparities Associated with Multisystem Inflammatory Syndrome in Children after SARS-CoV-2 Infection. Pediatr Infect Dis J. Sep 2022; doi: 10.1097/INF.0000000000003689
3. Galeotti C et al. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. Aug 2020; doi:10.1038/s41584-020-0448-7
4. Gruber CN et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). Cell. Nov 12 2020;183(4):982-995.e14. doi:10.1016/j.cell.2020.09.034

### Timeline of Index Event* for Cases and Controls




*Index event indicates date of MIS-C hospital admission (case-patients) and date of positive viral test ( controls).

### Relative Likelihood of Exposure among MIS-C Cases




### Population Attributable Risk

| Risk | Unadjusted PAR % | Unadjusted 95% CI | Adjusted[a] PAR % | Adjusted[a] 95% CI |
|---|---|---|---|---|
| Household member tested positive for SARS-CoV-2 | 26.9 | (15.5 -38.1) | 26.3 | (7.3 - 45.2) |
| Attendance at large event with≥ 10 people | 16.7 | (6.8 - 27.1) | 16.5 | (8.1 - 25.3) |
| Event was held indoors | 10.9 | (2.5 - 20.7) | 11.7 | (4.1 - 20.1) |
| Event was held indoors, limited masking | 7.0 | (1.9 - 14.4) | 8.0 | (2.7 - 15.5) |
| Household crowding (≥2 residents per room) | 12.4 | (2.5 - 22.9) | 13.5 | (3.6 - 24.2) |
| Public transportation | 13.2 | (4.8 - 22.9) | 13.4 | (7.4 - 19.7) |
| In-person school attendance, limited masking | 4.1 | (0.5 - 10.4) | 5.5 | (0.3 - 16.1) |
| OVERALL | 51.7 | (31.6 - 66.6) | 50.8 | (27.1 - 67.7) |

**CONTACT INFO**
**Laura D. Zambrano**
**lzambrano@cdc.gov**