Cardiology in the Young

cambridge.org/cty

Seasons of Kawasaki Disease during the COVID-19 pandemic

Todd T. Nowlen[1], Ashraf S. Harahsheh[2], Geetha Raghuveer[3], Simon Lee[4], Anji T. Yetman[5], Nagib Dahdah[6], Michael A. Portman[7], Supriya S. Jain[8], Michael Khoury[9], Selemet Tierney[10], Cedric Manlhiot[11], Pedrom Farid[12] and Brian W. McCrindle[12]

[1]Phoenix Children's, University of Arizona, Phoenix, AZ, USA; [2]Children's National Hospital, The George Washington University School of Medicine & Health Sciences, Washington, DC, USA; [3]Children's Mercy Hospital, Kansas City, MO, USA; [4]The Heart Center at Nationwide Children's Hospital, Columbus, OH, USA; [5]Children's Hospital and Medical Center, University of Nebraska Medical Center, Omaha, NE, USA; [6]CHU Ste-Justine, University of Montreal, Montreal, QC, Canada; [7]Seattle Children's Research Institute, Seattle, WA, USA; [8]New York Medical College-Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla, NY, USA; [9]Division of Pediatric Cardiology, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada; [10]Lucile Packard Children's Hospital, Palo Alto, CA, USA; [11]Blalock-Taussig-Thomas Congenital Heart Center at Johns Hopkins University, Baltimore, MD, USA and [12]Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada

Abstract

The incidence of Kawasaki Disease has a peak in the winter months with a trough in late summer/early fall. Environmental/exposure factors have been associated with a time-varying incidence. These factors were altered during the COVID-19 pandemic. The study was performed through the International Kawasaki Disease Registry. Data from patients diagnosed with acute Kawasaki Disease and Multiple Inflammatory Syndrome-Children were obtained. Guideline case definitions were used to confirm site diagnosis. Enrollment was from 1/2020 to 7/2023. The number of patients was plotted over time. The patients/month were tabulated for the anticipated peak Kawasaki Disease season (December–April) and non-peak season (May–November). Data were available for 1975 patients from 11 large North American sites with verified complete data and uninterrupted site reporting. The diagnosis criteria were met for 531 Kawasaki Disease and 907 Multiple Inflammatory Syndrome-Children patients. For Multiple Inflammatory Syndrome-Children there were peaks in January of 2021 and 2022. For Kawasaki Disease, 2020 began (January–March) with a seasonal peak (peak 26, mean 21) with a subsequent fall in the number of cases/month (mean 11). After the onset of the pandemic (April 2020), there was no clear seasonal Kawasaki Disease variation (December–April mean 12 cases/month and May–November mean 10 cases/month). During the pandemic, the prevalence of Kawasaki Disease decreased and the usual seasonality was abolished. This may represent the impact of pandemic public health measures in altering environmental/exposure aetiologic factors contributing to the incidence of Kawasaki Disease.

Introduction

Kawasaki Disease is the leading cause of acquired heart disease in children in developed countries.[1] While the aetiology of Kawasaki Disease remains unknown, a seasonal pattern has been well described in the northern hemisphere.[2,3] The incidence of Kawasaki Disease in North America has been shown to peak in the winter months (December through April) with a trough in late summer/early fall.[2,3] A seasonal environmental or infectious trigger is suspected as the cause for this pattern.[4] Seasonality has been reported to be greatest for the age group with the highest incidence, those between 0–4 years of age [3], possibly reflecting a developmental susceptibility to an immunological response modulated or triggered by seasonal factors.[4,5] In North America where this study was performed factors associated with an increased risk of Kawasaki Disease have included East Asian ethnicity, age < 4 years, higher pollution (nitrogen dioxide and sulphur dioxide), as well as higher rates for various types of infections.[3,5] While a decrease in the incidence of Kawasaki Disease during the COVID-19 pandemic has been reported in North America [6], Taiwan[7], Japan[8], and Korea[9,10] the impact of the pandemic on seasonality of Kawasaki Disease has not been investigated. Multisystem Inflammatory Syndrome-Children is a rare condition associated with SAR-CoV-2 and is a delayed hyperinflammatory condition occurring 2–6 weeks after an infection. Multisystem Inflammatory Syndrome-Children is characterised by multisystem involvement, resulting in organ dysfunction and shock. For Kawasaki Disease and Multisystem Inflammatory Syndrome-Children there is considerable overlap in presentation, clinical features,

Original Article

Cite this article: Nowlen TT, Harahsheh AS, Raghuveer G, Lee S, Yetman AT, Dahdah N, Portman MA, Jain SS, Khoury M, Tierney S, Manlhiot C, Farid P, and McCrindle BW (2024). Seasons of Kawasaki Disease during the COVID-19 pandemic. *Cardiology in the Young*, page 1 of 4. doi: 10.1017/S1047951124036047

Received: 14 April 2024
Revised: 7 October 2024
Accepted: 14 October 2024

Keywords:
Kawasaki Disease; seasons; COVID-19; multisystem inflammatory syndrome-children; paediatric inflammatory multisystem syndrome; international Kawasaki Disease Registry

Corresponding author:
Todd T. Nowlen;
Email: tnowlen@phoenixchildrens.com

management and early outcomes, with the primary differentiating factor being evidence of preceding SARS-CoV-2 infection or exposure.[11] We sought to determine the seasonal patterns of both Kawasaki Disease and Multisystem Inflammatory Syndrome-Children during and immediately following the COVID-19 pandemic.

Materials and methods

This study was performed through the International Kawasaki Disease Registry. Enrolled patients from each centre included all patients with a site diagnosis of either Kawasaki Disease or Multisystem Inflammatory Syndrome-Children. Each site obtained local ethics board approval, and enrollment and consent procedures were as locally approved, with many sites obtaining a waiver of consent. Data from patients were submitted into a centralised REDCap database, maintained by the data coordinating centre which operated under local ethics board approval and with data sharing agreements in place with each submitting site. The data coordinating centre confirmed the site diagnosis based on submitted information. American Heart Association guidelines were utilised for Kawasaki Disease[1] and for Multisystem Inflammatory Syndrome-Children, the 2020 Center for Disease Control guidelines with positive COVID-19 association were used for case verification.[12] As all sites were paediatric centres, adult patients more than 20 years of age were not included. Each diagnosis group was divided into either a confirmed or unconfirmed category based on the above criteria. Unconfirmed Kawasaki Disease was any patient for whom the site diagnosis could not be confirmed by the data coordinating centre (either because they had insufficient criteria or the submitted data were incomplete to confirm the diagnosis), or the patient had evidence of COVID-19 infection or exposure (hence, would overlap with Multisystem Inflammatory Syndrome-Children). Unconfirmed Multisystem Inflammatory Syndrome-Children was anyone for whom the site diagnosis could not be confirmed by the data coordinating centre, or they lacked evidence of a prior COVID-19 infection. Complete and uninterrupted data from prior to January 1, 2020 were not available. The number of patients for each diagnosis group per month was plotted over time. The number of patients/month for confirmed and unconfirmed Kawasaki Disease was tabulated for the anticipated peak Kawasaki Disease season (December–April) and the anticipated non-peak season (May–November). We have taken this to reflect the prevalence and not incidence, given that the denominator was not known and assumed to be the catchment area for each site.

Results

Data were included for 1975 patients from 11 large North American sites which had both verified complete data and uninterrupted site reporting (Toronto, Canada, 364 patients; Washington, DC, 261 patients; Kansas City, MO, 224 patients; Columbus, OH, 197 patients; Omaha, NB, 173 patients; Montreal, Canada, 149 patients; Seattle, WA, 143 patients; Phoenix, AZ, 134 patients; Valhalla, NY, 134 patients; Edmonton, Canada, 121 patients; Palo Alto, CA, 75 patients). For Kawasaki Disease, 531 patients met the diagnosis criteria with no evidence of COVID-19 infection or exposure, and there were an additional 389 patients for whom data were insufficient or discrepant to confirm the site diagnosis. For Multisystem Inflammatory Syndrome-Children, the diagnosis was confirmed for 907, and additionally, there were 148 patients for whom the data were insufficient or discrepant to confirm the site diagnosis. Demographic characteristics for confirmed and unconfirmed patients in both diagnosis groups are shown in Table 1.

Enrollment was from January 2020 to July 2023. Multisystem Inflammatory Syndrome-Children cases were first reported in North America in April. 2020 (Figure 1). There were peaks in January 2021 (96 patients) and January 2022 (87 patients) for confirmed Multisystem Inflammatory Syndrome-Children (mean monthly patients 21 for the entire time period) and much smaller associated peaks for unconfirmed Multisystem Inflammatory Syndrome-Children (peaks; 2020 = 29, 2021 = 9, 2022 = 7). For Kawasaki Disease, 2020 began (January–March) with a seasonal peak in Kawasaki Disease patients/month (peak 26, mean 21). However, there was a decrease in the number of Kawasaki Disease patients/month over the remaining time period (mean 11). Of note, however, there was a peak in unconfirmed Kawasaki Disease patients that corresponded with the first smaller peak of Multisystem Inflammatory Syndrome-Children cases in May 2020 suggesting some possible diagnostic confusion during this time period partially due to an initial lack of confirmatory testing for COVID-19. After the onset of the pandemic (April 2020) there was no clear seasonal variation for confirmed Kawasaki Disease (December–April mean 12 patients/month and May–November mean 10 patients/month), with a similar trend for unconfirmed Kawasaki Disease (December–April mean 10 patients/month and May–November mean 8 patients/month). However, long after the peaks in Multisystem Inflammatory Syndrome-Children, there appeared to be a later but smaller-than-expected peak of confirmed Kawasaki Disease in April 2023 (21 patients), followed by a subsequent decline in monthly patients.

Discussion

Our results show that during the pandemic in North America, the incidence of Kawasaki Disease decreased, and the usual seasonality was abolished. Early during the pandemic when no COVID-19 testing was available, there may have been overlap of Kawasaki Disease and Multisystem Inflammatory Syndrome-Children diagnoses. However, given the application and independent verification of the American Heart Association case definition and 2020 Center for Disease Control guidelines, the results are unlikely to be due to misclassification. Speculation regarding what might have affected the incidence and seasonal variability includes those factors most likely altered by the pandemic safety measures put in place (social distancing, staying home, reduction in travel, mask use, improved hygiene practices, etc.). Of the previously listed North American factors associated with increased risk of Kawasaki Disease, the primary factor affected by the pandemic safety measures is likely infectious disease exposure. In North America, numerous reports showed a decrease in the incidence of respiratory and gastrointestinal illnesses during the pandemic. At the onset of the pandemic in the United States the Center for Disease Control reported a 61% decrease in the number of clinical laboratory influenza specimens submitted pre-pandemic vs. during the pandemic and a 98% decrease in influenza as measured by the percentage of submitted specimens testing positive.[13] A multicentre study in 2021 demonstrated 64% lower odds of testing positive for respiratory syncytial virus and 46% lower for influenza.[14] New York City in 2022 documented a 70–90% reduction in the incidence of numerous respiratory viruses.[15] A study in Massachusetts demonstrated an 88% decrease in the daily

https://doi.org/10.1017/S1047951124036047 Published online by Cambridge University Press

Table 1. Demographiccharacteristics by diagnosis group

Variable	Kawasaki Disease Confirmed n=531	Kawasaki Disease Unconfirmed n=389	MIS-C Confirmed n=907	MIS-C Unconfirmed n=148
Sex, male (%)	315 (59%)	238 (61%)	582 (64%)	89 (60%)
Age (years)	3.0 (1.5, 5.3)	2.8 (1.2, 5.2)	8.6 (5.2, 12.2)	6.8 (2.8, 11.8)
Race/ethnicity	*n* = 372	*n* = 265	*n* = 691	*n* = 108
Black	57 (15%)	39 (15%)	204 (30%)	24 (22%)
White	171 (46%)	123 (46%)	263 (38%)	39 (36%)
East Asian	46 (12%)	28 (11%)	10 (1%)	4 (4%)
Hispanic	62 (17%)	44 (17%)	182 (26%)	28 (26%)
Other	36 (10%)	31 (12%)	32 (5%)	13 (12%)

Data are presented as frequencies (%)or median with values at the 25th and 75th percentiles (quartiles).
MIS-C, multisystem inflammatory syndrome-children.

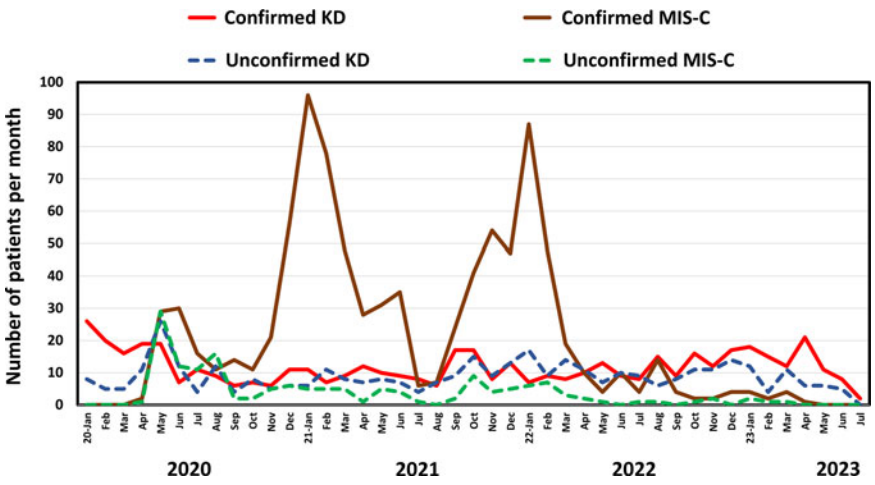

Figure 1. Monthly number of incident Kawasaki Disease and Multisystem Inflammatory Syndrome-Children patients. KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome-children.

diagnosis rate for gastroenteritis[16] and another in Colorado described a 52% decrease in outpatient acute gastroenteritis visits.[17] An exception to this was infection with respiratory syncytial virus, which showed a seasonal peak between July and November for 2021 and 2022[18] and an increase in hospitalisations in Canada.[19] This decrease in population exposure to infectious diseases may have resulted in a reduction in the incidence of Kawasaki Disease as well as its seasonality. Reluctance of Kawasaki Disease patients to seek hospital care during the pandemic, rather than the seasonality of Kawasaki Disease-related pathogen epidemics may be argued as a reason for the decrease in Kawasaki Disease incidence. While this study was not able to compare the number of days prior to diagnosis/hospitalisation pre- and post-pandemic there are a number of studies in North America,[20] Denmark,[21] and Japan[22] that have shown there was no difference in the number of days to presentation before and during the pandemic. An additional factor that may have been affected by the pandemic safety measures is pollution. A global study of pollution during the pandemic described a 20–30% reduction in NO_2 emissions, with 30% for the United States.[23] While it is true that there was a decrease in pollution during the pandemic, historically, one of the most common factors speculated to be involved is preceding viral infections, and this is the most likely contributing factor.[4] A further consideration may be that the decline in the number of Kawasaki Disease cases may have also been influenced by health care behaviour and health care system factors during the pandemic. Families may have been reluctant to present to sites, and accessibility to care may have been limited. This would lead to the assumption that an unknown number of patients with Kawasaki Disease would have the diagnosis missed. This is unlikely, given that Kawasaki Disease is an acute and serious condition, and also that there was likely heightened awareness of Kawasaki Disease-like illness during the pandemic given the emergence of Multisystem Inflammatory Syndrome-Children.

Just prior to the onset of the pandemic, the percentage of unconfirmed Kawasaki Disease (compared to total Kawasaki Disease cases) was lower than during the pandemic (23% vs 45% respectively). COVID-19 is speculated to result in immune system hyperactivity acting as a trigger for various hyperinflammatory diseases, potentially including Kawasaki Disease.[24] A portion of the unconfirmed Kawasaki Disease (who may have had exposure to COVID-19 with or without documentation) and the unconfirmed Multisystem Inflammatory Syndrome-Children patients may have been patients who experienced a hyperinflammatory reaction that did not fully manifest as a confirmed case for either condition. The number of Kawasaki Disease patients/month (both confirmed and unconfirmed) after the onset of the pandemic remained low, reflecting the reduced Kawasaki Disease incidence during the pandemic. Additionally, the trends for both the confirmed and unconfirmed Kawasaki Disease patients showed no seasonal variability. While some unconfirmed Kawasaki Disease patients may not have been Kawasaki Disease, if even a small percentage

https://doi.org/10.1017/S1047951124036047 Published online by Cambridge University Press

were true Kawasaki Disease seasonality still would have been seen, and this was not the case.

The primary study limitation is that data from prior to January 2020 were not available, as well as more recent data after the end of the pandemic. Therefore, comparisons were made to known historical trends and to the available months prior to the onset of the pandemic.

During both 2020 and 2021, the peak of confirmed Multisystem Inflammatory Syndrome-Children was seen during January which corresponds to the anticipated seasonal peak of Kawasaki Disease. This suggests that a COVID-19/Multisystem Inflammatory Syndrome-Children surge somehow replaced the Kawasaki Disease peak. However, debate continues regarding whether Multisystem Inflammatory Syndrome-Children is actually a specific form of Kawasaki Disease. Overall, these data show that during the pandemic in North America, the incidence of Kawasaki Disease decreased, and the usual seasonality was abolished. Further detailed epidemiologic data are needed to verify this observation, including ongoing surveillance to determine if seasonality returns.

Financial support. None.

Competing interests. The authors declare none.

References

1. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017; 135: e927–e999.
2. Burns JC, Herzog L, Fabri O, et al. Seasonality of Kawasaki disease: a global perspective. PLoS One 2013; 8: e74529.
3. Low T, McCrindle BW, Mueller B, et al. Associations between the spatiotemporal distribution of Kawasaki disease and environmental factors: evidence supporting a multifactorial etiologic model. Sci Rep 2021; 11: 1–13.
4. Rowley AH, Shulman ST. The epidemiology and pathogenesis of Kawasaki disease. Front Pediatr 2018. doi: 10.3389/fped.2018.00374.
5. Manlhiot C, Mueller B, O'Shea S, et al. Environmental epidemiology of Kawasaki disease: linking disease etiology, pathogenesis and global distribution. PLoS One 2018; 13: 1–17.
6. Sakai-Bizmark R, Estevez D, Wu F, et al. Kawasaki disease before and during the COVID-19 pandemic: a nationwide population-based study in the United States. Pediatr Infect Dis J 2023; XX: 1–7.
7. Yang YL, Kuo HC. Public health interventions for COVID-19 reduce Kawasaki disease in Taiwan. Children 2021; 8: 1–8.
8. Ae R, Makino N, Kuwabara M, et al. Incidence of Kawasaki disease before and after the COVID-19 pandemic in Japan: results of the 26th nationwide survey, 2019 to 2020. JAMA Pediatr 2022; 176: 1217–1224.
9. Kang JM, Kim YE, Huh K, et al. Reduction in Kawasaki disease after nonpharmaceutical interventions in the COVID-19 era: a nationwide observational study in Korea. Circulation 2021; 143: 2508–2510.
10. Kim BJ, Choi A, Kim HS, et al. Changes in the clinical characteristics of Kawasaki disease after coronavirus disease (COVID-19) pandemic: a database analysis. J Korean Med Sci 2022; 37: 1–12.
11. Harahsheh AS, Shah S, Dallaire F, et al. Kawasaki disease in the time of COVID-19 and MIS-C: the international Kawasaki disease registry. Can J Cardiol 2023; 40: 58–72. doi: 10.1016/j.cjca.2023.06.001.
12. Anon. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. 2020. Accessed December 16, 2023. https://emergency.cdc.gov/han/2020/han002432.asp.
13. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic — United States, Australia, Chile, and South Africa, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1305–1309.
14. Haddadin Z, Schuster JE, Spieker AJ, et al. Acute respiratory illness in children in the SARS-coV-2 pandemic: prospective multicenter study. Pediatrics 2021. doi: 10.1542/peds.2021-051462.
15. Yuan H, Yeung A, Yang W. Interactions among common non-SARS-CoV-2 respiratory viruses and influence of the COVID-19 pandemic on their circulation in New York City. Influenza Other Respir Viruses 2022; 16: 653–661.
16. Hatoun J, Correa E, Donahue S, Vernacchio L. Social distancing for COVID-19 and diagnosis of other infectious diseases in children. Pediatrics 2020. doi: 10.1542/peds.2020-006460.
17. Armistead I, Tran A, White A, Wilson E, Scallan Walker E. Trends in outpatient medical-care seeking for acute gastroenteritis during COVID-19 pandemic, 2020. Foodborn Pathogens and Disease 2022; 19: 290–292.
18. Anon. Increased Respiratory Syncytial Virus (RSV) Activity in Parts of the Southeastern United States: New Prevention Tools Available to Protect Patients. *Centers for Disease Control Health Alert Network*. 2023. Accessed January 13, 2024. https://emergency.cdc.gov/han/2023/han00498.asp.
19. Bourdeau M, Vadlamudi NK, Bastien N, et al. Pediatric RSV-associated hospitalizations before and during the COVID-19 pandemic. JAMA Netw Open 2023; 6: E2336863.
20. Burney JA, Roberts SC, Dehaan LL, et al. Epidemiological and clinical features of kawasaki disease during the COVID-19 pandemic in the United States. JAMA Netw Open 2022; 5: E2217436.
21. Ünlü AM, Holm M, Krusenstjerna-Hafstrøm T, Glerup M, Bjerre J, Herlin T. Changes in Kawasaki disease incidence and phenotype during the COVID-19 pandemic. Dan Med J 2023; 70: 3–10.
22. Katsumata N, Harama D, Toda T, et al. Prevention measures for COVID-19 and changes in Kawasaki disease incidence. J Epidemiol 2021; 31: 573–580.
23. Muhammad S, Long X, Salman M. COVID-19 pandemic and environmental pollution: a blessing in disguise? Sci Total Environ 2020; 728: 138820.
24. Zebardast A, Hasanzadeh A, Ebrahimian Shiadeh SA, Tourani M, Yahyapour Y. COVID-19: a trigger of autoimmune diseases. Cell Biol Int 2023; 47: 848–858.

https://doi.org/10.1017/S1047951124036047 Published online by Cambridge University Press