Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

An Unintended Consequence of Pandemic Control Measures: Fewer Cases of Kawasaki Disease

Shortly after the contours of the coronavirus disease 2019 (COVID-19) pandemic became apparent in early 2020, specific measures to reduce the risk of person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were implemented. By mid to late March 2020, recommendations for masking, social distancing, and school closures were in place in many areas, with other regions adopting these precautions later. By June 2020, it was recognized that these measures appeared to be impacting the transmission of other infectious agents of childhood, especially those spread by the respiratory route. Hatoun et al reported that substantially fewer children were diagnosed with streptococcal pharyngitis, nonstreptococcal pharyngitis, bronchiolitis, croup, influenza, and several other respiratory illnesses during calendar weeks 13-18 of 2020 compared with the same period in 2019.[1]

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Investigators at the Centers for Disease Control and Prevention recently reported that the circulation of respiratory viruses throughout the US has been greatly disrupted during the COVID-19 pandemic, with the magnitude, timing, and duration of this effect varying among viruses. Affected viruses include influenza, respiratory syncytial virus (RSV), endemic human coronaviruses, parainfluenza viruses, and human metapneumovirus, among others.[2] Similarly, in this volume of *The Journal*, Ae et also document sharp declines in many infections due to respiratory agents during the pandemic mitigation period.[3]

Shortly after publication of the report by Hatoun et al, we noted that fewer children were being diagnosed with Kawasaki disease at our institution compared with previous years.[4] We subsequently reported a 67% decline in Kawasaki disease diagnoses from April to December 2020 at our large children's hospital and a closely affiliated institution compared with cases diagnosed in the same months of the 8 prepandemic years 2012-2019: 13 cases in 2020, compared with the prepandemic annual mean of 46.6 cases ($P < .01$). Our updated data encompassing 12 full months from April 2020 through March 2021 indicate that this phenomenon has continued. This is of interest because a leading theory of the etiology of Kawasaki disease is that it is triggered by an as-yet unidentified ubiquitous respiratory agent, which likely also would be impacted by pandemic mitigation measures.[5]

At least 8 additional reports, including that by Ae et al and other reports from Korea, Singapore, Japan, Finland, and the US, also have documented substantially fewer cases of Kawasaki disease during the pandemic compared with prepandemic periods. These reports are summarized below.

Ae et al compared the prevalence of Kawasaki disease with that of RSV and exanthem subitum (roseola) because of the similar age distribution of the 3 conditions.[3] Since 1999, the Japanese government has conducted the National Epidemiology Surveillance of Infectious Diseases Program, in which the numbers of patients with specified common infectious diseases reported by ~3000 sentinel medical facilities across Japan are monitored weekly on the Web site of the Institute of Infectious Diseases. The investigators compared the differences in weekly numbers of cases of Kawasaki disease and pediatric infections in 2020 with those in 2017-2019. In weeks 15-35 of 2020, the number of cases of Kawasaki disease was 35% lower than the minimum in the comparable weeks of the previous years. Reductions in the number of cases of RSV (as much as 90% in weeks 19-43) also were seen, corresponding to school closures and persisting through 2020. The number of cases of Kawasaki disease remained as much as 60% lower from week 12 through 32 week compared with previous years. Rates of exanthem subitum changed little, presumably because this disease frequently is transmitted within the home by previously infected individuals.[6] In addition, there was no evidence that parents of children with Kawasaki disease were avoiding hospital visits in 2020, because the illness day of Kawasaki disease presentation did not change in 2020 compared with earlier years. It is highly unlikely that misdiagnosis of Kawasaki disease as multisystem inflammatory syndrome of childhood (MIS-C), a late complication of SARS-CoV-2 infection that has some overlapping clinical features with Kawasaki disease, could account for the reduced number of cases of Kawasaki disease during the pandemic. This is especially true in Asian countries, where MIS-C has been extremely rare.[7] However, to address this issue, the authors found that cases of incomplete Kawasaki disease did not increase in 2020, as might have occurred had MIS-C been misdiagnosed as Kawasaki disease. Because the number of cases of Kawasaki disease did not decrease as much as the number of cases of RSV, and because the prevalence of Kawasaki disease in unmasked children age

COVID-19	Coronavirus disease 2019
MIS-C	Multisystem inflammatory syndrome of childhood
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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<2 years did not decrease as much as it did for masked older children, the authors proposed that Kawasaki disease can be acquired both outside and within the home (from a previously infected sibling or parent). This theory is consistent with several other lines of evidence supporting a persistent infectious etiologic agent for Kawasaki disease.[8-10]

Kang et al studied all cases of Kawasaki disease diagnosed in children aged 0-19 years in Korea from January 2010 to September 2020 using the Korean National Health Insurance Service database.[11] February-September 2020 was defined as the period in which nonpharmaceutical interventions (eg, masking, distancing) were used to mitigate SARS-CoV-2 transmission. The incidence of Kawasaki disease during this period (18.8/100 000) was significantly lower than the annual mean incidence during the same months in the previous 10 years (31.5/100 000). This represents a 40% decline in cases of Kawasaki disease during the pandemic mitigation period. In children aged <4 years, the incidence declined from 123/100 000 in the prepandemic period to 80/100 000 during the pandemic mitigation period, a 35% decline. In 5- to 9-year-old children, the incidence of Kawasaki disease declined from a prepandemic rate of 23.8/100 000 to 10.6/100 000 during the pandemic mitigation period, a 55% decline. There was no significant change in Kawasaki disease incidence in the 10- to 19-year-old age group, in whom the incidence is much lower than in younger children.

Iio et al in Kobe, Japan compared the number of cases and incidence of Kawasaki disease before and during the COVID-19 pandemic in a retrospective cohort study from January 1, 2016 to December 31, 2020, encompassing all diagnoses of Kawasaki disease at the 18 Kobe hospitals with pediatric wards.[12] The cohort included 1027 children diagnosed with Kawasaki disease. The incidence of Kawasaki disease began to decline in April 2020, coincident with the onset of social distancing and masking measures. The number of cases of Kawasaki disease from April to December 2020 (n = 66) was 60% lower than the average from April to December (mean, n = 165) in 2016-2019. Annual Kawasaki disease incidence rates in children aged 0-4 years were 315/100 000 in 2016, 300/100 000 in 2017, 353/100 000 in 2018, 347/100 000 in 2019, and 188/100 000 in 2020. Substantial declines in 11 common pediatric respiratory infectious diseases also were observed beginning in April 2020, coinciding with the declaration of the pandemic emergency and school closures.

Chong et al in Singapore reported trends in Kawasaki disease before and during the COVID-19 pandemic at their 830-bed hospital, presenting data from 2017 to 2020.[13] Kawasaki disease admissions averaged 172.7 in 2017-2019, and totaled 126 in 2020, a decline of 27%. In children aged 2-5 years, the incidence of Kawasaki disease was 45% lower in 2020 than in the prepandemic years, whereas the incidence in children aged <2 years declined by only 12%, similar to the findings in Japan reported by Ae et al.

Bailey et al reported SARS-CoV-2 data from PEDSnet, a network of 7 large, widely scattered US pediatric hospitals and health systems that tested 135 794 pediatric patients for SARS-CoV-2.[14] That study also included the number of Kawasaki disease admissions from March 1 to May 1 in 2018 and 2019 to establish an at-risk denominator. Compared with 2018 and 2019 Kawasaki disease case counts, there was a 40% decrease in 2020 case counts across all 7 health systems (n = 259 in 2020, 430 in 2019, and 433 in 2018). At least 6 of the 7 hospital systems had substantially fewer cases of Kawasaki disease in 2020 compared with the 2 prepandemic years.

Phamduy et al reported data from the Pediatric Health Information System database compiled by the Children's Hospital Association partnering with 51 US children's hospitals to assess first hospitalizations for Kawasaki disease in 2016-2020.[15] Kawasaki disease hospitalizations were stable from 2016 to 2019 (mean, 1722/year) but declined by 20% in 2020 (n = 1383). A peak of Kawasaki disease diagnoses in May 2020 was attributed by the authors to likely misdiagnosis of MIS-C. They reached this conclusion based on several factors, including the increased median age of patients with reported Kawasaki disease, the increase in intensive care unit admissions, and the altered demographics of cases of Kawasaki disease, with increases in white and Hispanic children and a decrease in Asian children in 2020 compared with 2016-2019. These data suggest that the decline in cases of Kawasaki disease in 2020 in this administrative database was effectively underestimated.

Masaru Terai from Chiba Municipal Kaihin Hospital, Tokyo examined the number of patients with Kawasaki disease for 2017-2020 at his institution (personal communication). Annual January-December Kawasaki disease totals for 2017-2019 ranged from 93 to 99 (mean, 96), and for 2020, the total was 76, a 21% decline. More accurately reflecting the peak period of COVID-19 activity in Japan, the number of cases of Kawasaki disease ranged from 68 to 70 (mean, 69) in May-December 2017-2019 and 30 in the same period in 2020, a 56% decline.

While this editorial was in press, Koskela et al in Finland reported a decline in respiratory infections and a 51% decline in Kawasaki disease cases during the pandemic, suggesting that a transmissible microbe is responsible for Kawasaki disease and that social distancing has a protective effect.[16]

Epidemiologic studies over the last 50 years have supported a ubiquitous infectious agent as the cause of Kawasaki disease.[17] These features include the rarity of cases in children age <6 months with a sharp increase in prevalence at 6-12 months, consistent with increasing susceptibility following a decline in passive maternal antibody protection. The highest prevalence in young children followed by a decreased prevalence after age 6 years and the virtual absence of cases in adults supports a common infection that most often is asymptomatic or mildly symptomatic but can result in Kawasaki disease during young childhood. The frequent epidemics and outbreaks of Kawasaki disease worldwide also support a ubiquitous infectious agent as the cause, as does the typical winter-spring seasonality of Kawasaki disease. Identifying person-to-person transmission of a ubiquitous yet subclinical infectious agent can be difficult, but the existence of secondary sibling cases of

Kawasaki disease generally occurring within 10 days of the index case, and a report of likely person-to-person transmission in a highly susceptible population within a small geographic area, support this possibility.[18] The rarity of recurrence of Kawasaki disease is consistent with infection followed by subsequent immunity and argues against a theory of multiple diverse etiologic triggers for Kawasaki disease or an autoimmune pathogenesis. The prominent immunoglobulin A inflammatory response associated with Kawasaki disease supports the respiratory tract as the portal of entry for an infectious agent.

We have demonstrated that plasmablasts, the precursors to antibody-producing plasma cells, are clonally expanded in the peripheral blood of children with Kawasaki disease at 1-2 weeks after fever onset, indicating an antigen-driven immunologic response to a recent infection.[5] We further demonstrated that these plasmablasts encode antibodies that recognize antigen in intracytoplasmic inclusion bodies in ciliated bronchial epithelial cells of children who died of Kawasaki disease.[5] These results support clinical, epidemiologic, ultrastructural, and RNA evidence that suggests a novel ubiquitous respiratory virus as the cause of Kawasaki disease.[19] It seems logical that transmission of this agent also would be reduced by school closures, masking, and social distancing. Other potential explanations for the decline in cases of Kawasaki disease appear to have been ruled out; in particular, there has been no decrease in diagnosis of other serious medical conditions, such as urinary tract infections/pyelonephritis,[4,13] a lack of delayed diagnosis of Kawasaki disease,[3,4] and a lack of potential confusion with MIS-C[3,4] (which is rare in Asia) during the period of pandemic mitigation.

It is ironic that several of the studies of Kawasaki disease in the COVID-19 era initially aimed to investigate the possibility that SARS-CoV-2 could be a trigger for Kawasaki disease. Aggregate data do not support this premise, and in fact provide convincing support for a declining incidence of Kawasaki disease during the period of pandemic mitigation in several countries, coincident with declines in transmission of common pediatric respiratory pathogens. The decreased prevalence of Kawasaki disease with masking and social distancing has led to increased understanding of the epidemiology and likely etiology of Kawasaki disease. This unintended consequence of pandemic mitigation provides additional support for an as-yet unidentified novel common pediatric respiratory virus that could result in persistent infection as the etiology of Kawasaki disease, as suggested by Ae et al, and may help direct Kawasaki disease research toward uncovering the causative agent. ■

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Respiratory Syncytial Virus and Influenza Infections: The Brain is Also Susceptible

Viruses are a ubiquitous part of childhood, and though commonly mild, there is a more perilous side to common childhood viral infections. Childhood "viral syndromes" may begin with fever, cough, and rash; however, by poorly understood mechanisms, the generally mild viral infection can progress to cause severe neurologic complications. Important endemic respiratory infections—respiratory syncytial virus (RSV) and influenza occur each fall and winter. These 2 viruses cause significant respiratory morbidity and are leading causes of hospitalization for respiratory failure in pediatric hospitals each year.[1-3] With about 58 000 pediatric hospitalizations for RSV and up to 26 000 hospitalizations for influenza in a given year, rare complications can be meaningful to parents and physicians caring for these patients.[2,3] In this volume of *The Journal*, 3 separate studies confirm and extend our understanding of the neurologic complications of RSV and influenza, and characterize their association with risk factors and resource utilization.[4-6]

See related articles, p 24, p 32, and p 39

Neurologic complications of influenza were described as early as the late 1890s as a clinical syndrome, generally in children, of stupor, possible seizures, paralysis, and oculomotor palsies. Post-mortem brain examinations revealed hemorrhage and sinus venous thromboses. This clinicopathologic diagnosis was termed "Strumpell-Leichtenstern encephalitis."[7] Reports of neurologic complications of influenza continued to evolve into modern times, with variability in severity and frequency associated with specific strains, most recently H1N1.[8,9] Antoon[6] and Frankl,[5] and their research teams present findings from 2 different datasets of patients hospitalized with influenza, one extracted from Pediatric Health Information System, a multicenter pediatric administrative database, and the other, a historical cohort from a single large tertiary care pediatric hospital. Both groups excluded neonates, and included infants throughout adolescence, who carried either a discharge *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* diagnosis of influenza within the Pediatric Health Information System database or who had a positive influenza polymerase chain reaction during hospitalization within the timeframe of the historical cohort. Their combined total of >30 000 patients had similar findings: approximately one-tenth of their respective cohorts manifested neurologic complications. Seizures and encephalopathy were the most common neurologic complications, and children with chronic/pre-existing neurologic conditions were at particular risk for any neurologic complication.

The neurologic complications of RSV infection are most commonly described in case reports and case series. Saravanos et al undertook a systematic review that included articles that included patients <15 years old with RSV-associated severe acute neurologic complications.[4] To capture only severe disease, they excluded simple febrile seizures and isolated apnea. Within the 87 studies included, seizures and encephalopathy were the most common neurologic complications of this respiratory infection. They extracted individual cases from their included studies and derived 150 patients, added an additional 5 patients from the Australian Acute Childhood Encephalitis prospective cohort study, and again found that seizure, decreased level of consciousness, and encephalopathy were the most common neurologic features.

Within these 3 reports, the presence of neurologic complications from RSV or influenza infection was associated with increased hospital resource utilization, including higher intensive care unit admissions and increased medical therapies (antiviral or immunomodulatory), and a risk for neurologic dysfunction at time of discharge.[4-6] Some of the rare, more severe neurologic complications including fulminant cerebral edema, infarction, meningitis/encephalitis, and paralysis, readily lend themselves to longer and more complicated hospitalizations.

The mechanisms that cause these neurologic complications in RSV and influenza are unclear. Viral febrile illnesses in young children and metabolic derangements from dehydration or syndrome of inappropriate antidiuretic hormone secretion can cause seizures and encephalopathy,

CNS Central nervous system
CSF Cerebrospinal fluid
RSV Respiratory syncytial virus

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