Kawasaki-like disease: emerging complication during the COVID-19 pandemic

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Children have to date borne a minimal medical burden in the global COVID-19 pandemic. Epidemiological data from many countries show that children are a small minority of those who test positive. Children younger than 18 years have made up only 1·7% of national cases in the USA,[1] 1% of cases in the Netherlands,[2] and 2·0% of a large observational cohort in the UK.[3] Whether these proportions reflect lower susceptibility among children versus adults,[4] or similar infection rates, but much higher proportions with asymptomatic disease, is unclear.[5] Studies from several countries have confirmed that severe illness and death due to COVID-19 among children are rare,[1,6] with accurate estimates unavailable because of an absence of true population denominators. Attention has now shifted to the vulnerability of children for two reasons. First, the degree to which children transmit COVID-19 is key to how countries reopen communities after lockdown. Second, new concerns about a novel severe Kawasaki-like disease in children related to COVID-19, including Lucio Verdoni and colleagues'[7] description of an outbreak in Italy in *The Lancet*, change our understanding of this disease in children.

Kawasaki disease is a rare acute paediatric vasculitis, with coronary artery aneurysms as its main complication. The diagnosis is based on the presence of persistent fever, exanthema, lymphadenopathy, conjunctival injection, and changes to the mucosae and extremities.[8,9] Verdoni and colleagues describe ten cases (seven boys, three girls; aged 7·5 years [SD 3·5]) of a Kawasaki-like disease occurring in Bergamo, Italy, at the peak of the pandemic in the country (Feb 18 to April 20, 2020), a monthly incidence some 30-fold higher than observed for Kawasaki disease across the previous 5 years. Bergamo was the city with the highest rate of infections and deaths in Italy at that time. Within the cluster were five children who had features similar to Kawasaki disease (ie, non-purulent conjunctivitis, polymorphic rash, mucosal changes, and swollen extremities); however, another five children presented with fewer than three of the diagnostic clinical signs and were older than patients with classic Kawasaki disease. There was also a high proportion of shock, with five of ten children presenting with hypotension requiring fluid resuscitation, and two of ten children needing inotropic support . Two of ten children had a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR swab and eight of ten had a SARS-CoV-2-positive serology test; however, these tests were not done contemporaneously with the episode, so the clinical relevance is unclear. The majority of patients with Kawasaki disease respond well to intravenous immunoglobulin; however, 10–20% require additional anti-inflammatory treatment.[9] In this cohort, eight of ten children received high-dose corticosteroids in addition to intravenous immunoglobulin. These differences raise the question as to whether this cluster is Kawasaki disease with SARS-CoV-2 as the triggering agent, or represents an emerging Kawasaki-like disease characterised by multisystem inflammation. The diagnosis of Kawasaki disease is based on clinical and laboratory criteria and is hindered by the lack of a diagnostic test. Understanding the pathophysiology of this emerging phenomenon might provide welcome insights into our understanding of Kawasaki disease.

Anecdotally, clinicians across Europe have identified clusters of similar cases. In the UK, paediatricians have identified a small group of children presenting with shock and a multisystem inflammation to critical care units, some of whom have coronary artery aneurysms, and a further group of less severely ill children with a Kawasaki-like disease, who respond to a variety of immunomodulatory treatments, including intravenous immunoglobulin, corticosteroids, and biologics such as infliximab and anakinra (Whittaker E, unpublished). Long-term echocardiogram data on coronary artery aneurysms are pending. In response to this cluster in London, UK, we notified the National Health Service of the emergence of an unusual disorder, and an alert was issued on April 25. On the basis of the review of clinical and laboratory features, a case definition of the syndrome we have provisionally called paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was formulated by experts in the UK and published by the Royal College of Paediatrics and Child Health.[10] Correspondence[11] in *The Lancet* on May 7, 2020, describing nine children

with PIMS-TS requiring critical care in south London highlights the severe end of the spectrum of this disease.

The recognition of this disease late in the first pandemic wave might relate to its rarity and the difficulty of recognising uncommon syndromes in fragmented health-care systems rapidly reorganising to deal with a pandemic. Alternatively, it might reflect a mechanism for PIMS-TS. Alternatively, it suggests that the mechanism for the Kawasaki-like disease described here and PIMS-TS might represent post-infectious inflammatory syndrome, which might be antibody or immune-complex mediated, particularly because in this Italian cohort there was little evidence of viral replication. For prospective studies, measuring antibody at the time of presentation, as well as consenting patients for appropriate research samples, will be essential to elucidate the mechanism of this syndrome.

Although the Article suggests a possible emerging inflammatory syndrome associated with COVID-19, it is crucial to reiterate—for parents and health-care workers alike—that children remain minimally affected by SARS-CoV-2 infection overall. Understanding this inflammatory phenomenon in children might provide vital information about immune responses to SARS-CoV-2 and possible correlates of immune protection that might have relevance both for adults and children. In particular, if this is an antibody-mediated phenomenon, there might be implications for vaccine studies, and this might also explain why some children become very ill with COVID-19, while the majority are unaffected or asymptomatic.

In the UK, a British Paediatric Surveillance Unit study has been rapidly opened to explore the extent of PIMS-TS nationally. Two COVID-19 priority studies in the UK (DIAMONDS [Central Portfolio Management System 45537] and ISARIC [UK Clinical Research Network 14152]) are collaborating to ensure that every child with this emerging syndrome has the opportunity to consent to take part in a study exploring mechanisms. International discussions are underway to facilitate standardised approaches to the investigation and management of these children, including treatment strategies to prevent long-term adverse outcomes such as coronary artery aneurysms.

For the **DIAMONDS study** see https://diamond-project.eu/consortium/

For the **ISARIC study** see https://isaric.tghn.org/clinical-characterisation-protocol-ccp/

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