



# Kawasaki disease: the most common cause of acquired heart disease among children globally

Rakesh Kumar Pilia<sup>1</sup>, Adriana H. Tremoulet<sup>2,3</sup>, Shankar Prinja<sup>4</sup>, Nagib Dahdah<sup>5</sup>   
and Surjit Singh<sup>1</sup> 

## Editorial

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### Corresponding author:

Surjit Singh;

Email: [surjitsinghpgi@rediffmail.com](mailto:surjitsinghpgi@rediffmail.com)

<sup>1</sup>Pediatric Allergy and Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India; <sup>2</sup>Kawasaki disease Research Center, Department of Pediatrics, University of California San Diego, La Jolla, CA, USA; <sup>3</sup>Rady Children's Hospital-San Diego, San Diego, CA, USA; <sup>4</sup>Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research, Chandigarh, India and <sup>5</sup>Department of Pediatric Cardiology, CHU Sainte-Justine, University of Montreal, Montreal, QC, Canada.

## Abstract

Kawasaki disease is a childhood vasculitic disorder that has a special predilection for coronary arteries. Kawasaki disease has been reported from all regions of the world, with an increasing incidence in several countries. Kawasaki disease is now the most common cause of acquired heart disease in children all over the world. However, it is concerning that the estimated vast majority of Kawasaki disease cases in low- and middle-income countries are not getting diagnosed and treated. The World Health Organization acknowledges cardiovascular disease in their priority of actions. The World Health Organization is invited to acknowledge the reality of Kawasaki disease in its list of cardiovascular diseases and take steps to facilitate the diagnosis and treatment of Kawasaki disease, especially in low- and middle-income countries. It is a disease of public health importance and needs urgent prioritisation by the World Health Organization.

## An overview of the emergence of Kawasaki disease

Kawasaki disease is a paediatric vasculitic disorder that has a special predilection for coronary arteries. Kawasaki disease commonly occurs in preschool children, but older children, and rarely adults, can also be affected. It is a serious and potentially life-threatening condition, which results in the development of coronary artery aneurysms in up to 25% of untreated patients. The risk of coronary artery aneurysms is reduced to <5% with prompt and appropriate treatment.<sup>1</sup> When Kawasaki disease occurs in infants, as many as 50% may go on to develop coronary artery aneurysms.<sup>1,2</sup> Kawasaki disease carries acute and long-term consequences on children's health, cardiac viability, families' welfare, and public health management. The condition has been reported from all regions of the world, with an increasing incidence in several countries.<sup>3,4</sup>

Myocardial involvement (myocarditis), thought to be universal in Kawasaki disease, may be severe enough to lead to cardiogenic shock.<sup>5</sup> Coronary artery aneurysms may get thrombosed in the acute stage and lead to myocardial infarction.<sup>1</sup> Long-term cardiac complications of Kawasaki disease include the risk of premature acute coronary syndrome and myocardial infarction in children and young adults, arrhythmias, congestive cardiac failure, and sudden death.<sup>2</sup> Early diagnosis and optimal treatment of Kawasaki disease results in a substantial decrease in long-term cardiovascular complications associated with the disease, thereby resulting in lower healthcare costs.<sup>6</sup>

Kawasaki disease has important public health implications because of the significant long-term cardiac morbidity associated with it.<sup>1</sup> While there are no known means to prevent the occurrence of Kawasaki disease, early diagnosis and treatment can lead to effective disease control and prevention of serious complications, such as the development of coronary artery aneurysms, thrombosis, and myocardial infarction. The key challenge faced by health professionals in low- and middle-income countries in Africa, the Middle East, Latin America, and the Southeast Asia Region is in securing early diagnosis and ensuring access to appropriate treatment with intravenous immunoglobulin.<sup>7</sup> There is reason to believe that a substantial number of Kawasaki disease cases in these countries are, at present, not getting diagnosed and inherently not treated.<sup>7</sup>

## Epidemiology of Kawasaki disease in economically developed countries

Epidemiological data from Europe, North America, Japan, and Australia clearly show that Kawasaki disease has replaced acute rheumatic fever as the most common cause of acquired heart disease in children.<sup>1</sup> The reported incidence of Kawasaki disease in Japan prior to the

COVID-19 pandemic was 371/100,000 children below 5 years old.<sup>8</sup> Japan reports as many as 14,000 children with Kawasaki disease every year, and the number increases annually despite a falling birth rate. According to the latest estimates from Japan, approximately 1 in every 64 boys and 1 in every 80 girls will develop Kawasaki disease during the first 10 years of their life.<sup>4</sup> Korea and Taiwan have incidence rates of 194.7 and 69.5/100,000 children below 5 years, respectively, while in Europe, the incidence ranges from 5 to 20/100,000 children below 5 years. In the United States, despite some seasonal variations in Kawasaki disease, incidence rates are 20–25/100 000 children below 5 years. Despite a lower incidence, it is estimated that 1 in 1600 Americans will have a history of childhood Kawasaki disease by 2030. While countries like Japan, Korea, and Taiwan have continued to report a steadily increasing incidence of Kawasaki disease over the last 3 decades, the incidence has plateaued off in North America and most European countries.<sup>3,4</sup>

### Epidemiology of Kawasaki disease in low-income and middle-income countries

While there is a paucity of literature on the epidemiology of Kawasaki disease in Africa, there is an increasing number of reports on Kawasaki disease from the Middle East and Latin America.<sup>4</sup> There are also published data to suggest that Kawasaki disease is now being increasingly recognised in India and China – two countries that together comprise more than one-third of the world's population. Although nationwide data on the incidence of Kawasaki disease are not available from either of the two countries, city-specific incidence data have been published from both countries.<sup>3,9,10</sup>

The first epidemiological study from North India documented the increasing incidence of this condition from 1994 (0.51/100,000) to 2008 (4.54/100,000) in children below 15 years.<sup>9</sup> The second epidemiological study covered the period 2009–2014 and showed that the incidence of Kawasaki disease in children below 5 years was 5.35/100,000.<sup>10</sup> Incidence rates of Kawasaki disease in Chandigarh, India, during 2015–2019 varied from 5.64 (in 2015) to 9.72 (in 2019) per 100,000 children below 5 years.<sup>11</sup> The trend analysis from this Indian study, from 1994 to 2019, revealed a statistically significant increase in Kawasaki disease cases in children <5 years (1.4/100,000 to 9.87/100,000) and <15 years (0.54/100,000 to 5.07/100,000). Incidence data for Kawasaki disease are available from several cities in China. While a study from Shanghai (2017) reported an incidence of 107.3/100,000 children <5 years, in Beijing (2004) the incidence was 55.1/100,000 children <5 years. Sichuan (2011) reported a much lower incidence – 7.1/100,000 children <5 years. The incidence of Kawasaki disease in Hong Kong SAR (2011) was 74/100,000 children <5 years.<sup>3</sup> Data on Kawasaki disease incidence are not available in the western and northern parts of China. Because of the difficulties in establishing a confirmatory diagnosis, especially in low-income and middle-income countries, the actual burden of Kawasaki disease may be much higher. Besides the health impact, households with children suffering from Kawasaki disease are also likely to have significant financial hardship. While there is scarce evidence in the context of Kawasaki disease, there is enough evidence to suggest the catastrophic outcomes and impoverishment as a result of cardiovascular disorders (including coronary artery disease and myocardial infarction) in low-income and middle-income countries.<sup>12,13</sup>

There is evidence to suggest that the incidence of acute rheumatic fever in India (as also in other low-income and middle-income countries) has decreased significantly and continues to show a declining trend.<sup>14</sup> This has probably resulted from increased awareness amongst the healthcare professionals, the implementation of preventive measures (e.g., improved housing and living conditions), and early treatment of streptococcus A infection with antimicrobials. To put in perspective, in the absence of a causative agent(s) or preventive measures for Kawasaki disease to implement, it is predicted that while acute rheumatic fever cases would continue to decrease, the incidence of Kawasaki disease is likely to increase further as awareness of the disease becomes widespread and the probability of diagnosis becomes optimal.

### Kawasaki disease and healthcare planning

It is concerning that the estimated vast majority of Kawasaki disease cases in low-income and middle-income countries are not getting diagnosed and treated. Over the last 3 decades, Kawasaki disease has gradually emerged as the leading cause of acquired heart disease in children the world over.<sup>1</sup> Kawasaki disease should, therefore, no longer be considered a disease only of more affluent populations – it has public health implications for all countries.<sup>3</sup> The consequences of unrecognised, and hence untreated, Kawasaki disease in childhood may manifest decades later as complex acute coronary syndrome.<sup>1</sup> This has important implications for healthcare planners.

The World Health Organization acknowledges cardiovascular disease in their priority of actions. The World Health Organization is invited to acknowledge the reality of Kawasaki disease in its list of cardiovascular diseases and take steps to facilitate the diagnosis and treatment of Kawasaki disease, especially in low-income and middle-income countries. The sustainable development goals target 3.2 is to reduce the under-5 mortality rate to 25 or less per 1000 live births. Based on the current trends, it is likely that nearly 60 countries globally will not achieve their target. Kawasaki disease is emerging as the most important cause of acquired heart disease in children and has serious adverse consequences, including death, if it remains undiagnosed and untreated. However, the challenge so far has been the lack of credible data for policymakers and national programme managers to make decisions.

The World Health Organization's core function is evidence generation and provision of technical advice to countries. First, it will be crucial for World Health Organization and partners to generate evidence on the global burden of Kawasaki disease in children less than 5 years. The World Health Organization can also help by increasing awareness about Kawasaki disease amongst healthcare professionals and the public at large and by including Kawasaki disease in the priority areas for health. This will aid in developing and strengthening surveillance systems, especially in the low-income and middle-income countries. At the country level, this may encourage policymakers to include Kawasaki disease in the list of diseases that are included in routine surveillance and get notified. Further, World Health Organization can take the lead in developing a framework to support programme managers/ministries of health in developing expertise and building capacity of tertiary management services for Kawasaki disease (including diagnosis, treatment, and follow-up) into health systems in low-income and middle-income countries. This would, in turn, decrease the risk of the development of serious complications (majorly, coronary artery aneurysms, myocarditis, myocardial infarction, and death) of Kawasaki disease. Several low-

income and middle-income countries would need the support of World Health Organization to ensure access to, and availability of, intravenous immunoglobulin which is the standard of care for Kawasaki disease.<sup>1</sup> Early diagnosis and optimal treatment of Kawasaki disease results in a substantial decrease in long-term cardiovascular complications associated with the disease, thereby resulting in lower healthcare costs.

During the SARS-CoV-2 pandemic, the emergence of a new syndrome, the Multisystem Inflammatory Syndrome of Children, was rather rapidly put in check thanks to five decades of experience with, and research on Kawasaki disease.<sup>15</sup> Whereas Multisystem Inflammatory Syndrome of Children has eclipsed, Kawasaki disease remains a global concern in the absence of a clear cause and in the absence of preventive measures or vaccines.

## Conclusions

Kawasaki disease is now the most common cause of acquired heart disease in children all over the world. The incidence is rising, surpassing rheumatic heart disease throughout the globe. It is a disease of public health importance and needs urgent prioritisation by the World Health Organization.

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