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Editorial

Fostering Global Collaboration Around Kawasaki Disease. Reflections From the 14th International Kawasaki Disease Symposium

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On August 26 to August 29, the 14th International Kawasaki Disease Symposium (IKDS) took place in Montreal, Canada. This symposium, first held in 1984 in Hawaii, represents a long-standing history of an international meeting where clinicians and scientific investigators passionate about Kawasaki disease (KD) gather to share and solve the mysteries of a half-a-century-old acute inflammatory disease of childhood that can have life-threatening coronary artery complications.[1] The disease, initially described by a constellation of its clinical features (the mucocutaneous lymph node syndrome), carries the name of Doctor Tomisaku Kawasaki, the astute clinician who first described a cohort of 50 children in 1967. Since then, KD has grown to be the most common cause of acquired heart disease in most regions of the world.[2–5] However, it is still a disease that is underserved in many parts of the world, with limited resources available to study its cause, bring diagnostic tools to market in partnership with industry sponsors, and develop new therapies. Given this, children with KD are still at high risk of being misdiagnosed or not having access to treatments to prevent life-threatening coronary artery aneurysms. In spite of all of this, clinicians, scientists, and patient advocates have been working for over 50 years to advance the care of children with KD worldwide. The scientific endeavours have ranged from animal to clinical research and from genetics to anthropology. The advances in KD research have helped improve pediatric health beyond just KD, as recently evidenced by the use of novel anti-inflammatory therapies whose safety had been proven in KD for multisystem inflammatory syndrome in children triggered by the SARS-CoV-2 virus.[6–8]

The passing of *Sensei* Kawasaki in June of 2020 marked an important moment in the history of KD. The 14th IKDS was an opportunity to honor Dr Kawasaki's memory and galvanize a new generation of young investigators from around the world. Therefore, we, the co-chairs of the 14th IKDS, dedicated this meeting to fostering global collaboration around KD.

In preparation for the meeting, we created the website IKDS.org. There was previously no central location on the internet for KD. Now IKDS.org serves as a central repository of KD statements and guidelines from 11 countries in multiple languages as well as a central location to find KD foundations from 8 countries that can help families with children newly diagnosed with KD connect with regional support groups and other KD families.[9,10] We anticipate that this website will grow to be a hub for current and future collaborative groups to share their upcoming activities and meetings and for patient advocacy foundations to intersect with KD scientific networks.

Indeed, KD has become a global problem with increasing incidence in countries such as in Europe, India, and Japan. With new advances in diagnosis and therapeutics, children with KD with giant aneurysms are surviving into adulthood and now must be seen by adult cardiologists.[4,11–18] In addition, advances in understanding the complex genetics of KD, the use of artificial intelligence science to better diagnose KD, and the changes in assessing coronary lesion severity lead us to new ways to approach KD (Fig. 1).

KD is in the rare diseases category, defined by affecting fewer than 200,000 people in the United States or fewer than 1 in 2000 people in Europe.[19–21] But truly, is KD that rare? How rare can a disease be if 1 in 1600 Americans will have a history of childhood KD by 2030 and if 1 in every 65 boys and 1 in every 82 girls are diagnosed with KD in Japan.[22–24] Perhaps "orphan" is the best descriptor of KD. KD is common enough to affect children every day, but not prevalent enough to allow discovering genetic determinants with the strongest statistical power, for instance. Not too frequent to allow massive clinical trials or comparative randomized clinical management of acute coronary artery syndrome.[25–28] The most dramatic orphan status of KD is evidenced by the

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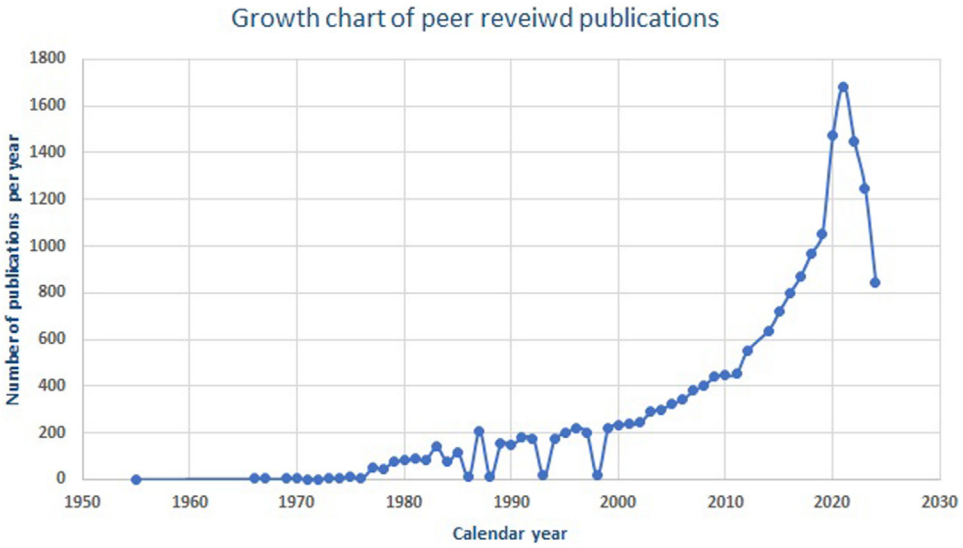

Figure 1. Growth chart depicting incremental annual peer-reviewed scientific publications on Kawasaki disease. The drop in the last 3 years is likely due to the decrease in publications where KD is compared to Multisystem Inflammatory Syndrome in Children, the inflammatory syndrome triggered by SARS CoV-2. 2024 publications not represented due to being incomplete at the time of interrogation (August 2024). Note: dips between 1980 and 2000 are not zero; they are simply low numbers below 50 publications per year. Generated from data available in PubMed.

paucity of funds available to conduct research on the disease, and even more in partnering with industry to convert scientific diagnostic platforms into readily available clinical tests.

Recently we faced the seemingly insurmountable hurdle of raising funds to support IKDS. However, we forged ahead and were able to raise sufficient capital to host this event in Montreal. After 3.5 days of lively discourse, focusing on regional hurdles on diagnosis and treatment, genetics, epidemiology, basic science, imaging, novel therapeutics, immunology, and long-term care, new collaborative projects arose. The agenda included new elements, such as panelists from around the world debating the treatment of an infant with KD, and breakout sessions on the following topics: research career planning, hands-on echocardiography coronary scanning, pathology and histology showcasing, clinical case vignettes with the experts, and patient/parental advocacy groups meet the experts. The last day culminated in celebration of young investigators, a memorial to the late *Sensei* Tomisaku Kawasaki, and a town hall meeting around building an international society focused on KD. A key panel

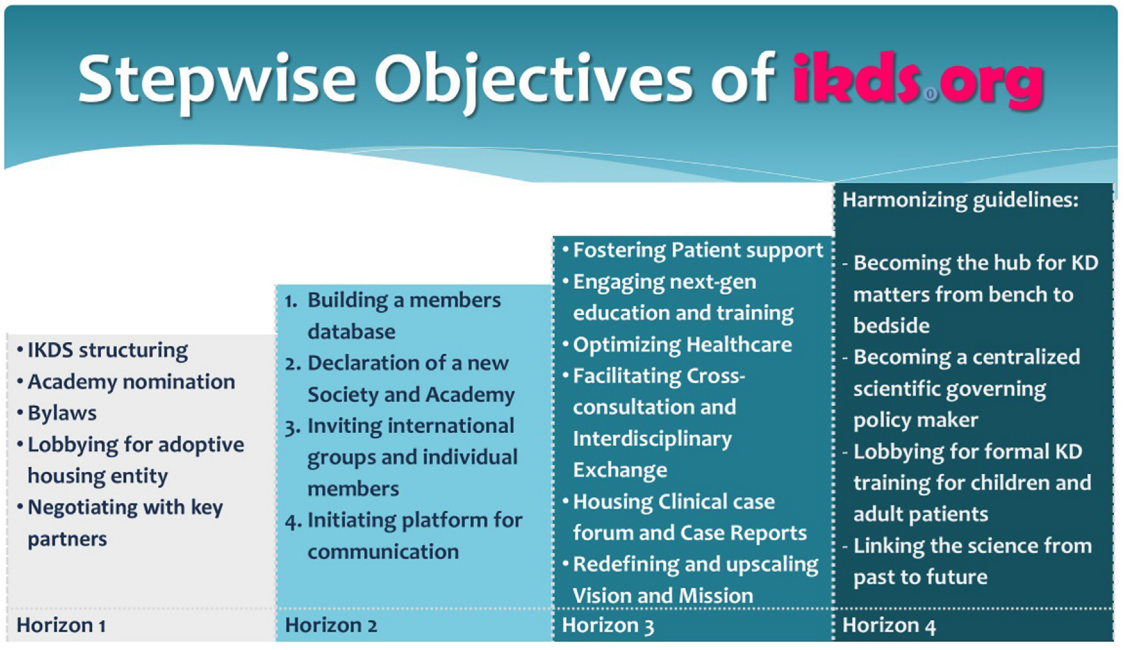

Figure 2. The vision in creating an international Kawasaki disease society relies on a stepwise approach, with objectives set over 4 horizons. IKDS, International Kawasaki Disease Symposium.

discussion that led to a new project focused on a comparison of several coronary artery *Z*-score calculators. In the area of novel therapeutics, there are now several treatment options for treatment resistance or children with coronary artery aneurysms, though there is still clinical equipoise as to which treatment combination is best. There is likely never to be a clinical trial that can determine the best therapeutic course for these patients as it would likely be underpowered and would be difficult to fund. Thus, there is now interest in creating a registry from multiple centres around the world to find the most effective treatment, much as was done with the Best Available Treatment Study for multisystem inflammatory syndrome in children.[29]

Beyond the exchange of science at the 14th IKDS, we, the co-chairs of the symposium, had envisioned the event to be transformational. For the past 40 years, IKDS has brought together a large body of research and housed a family of scientists around the disease with a thirst to find solutions and establish the best practices to conquer the many mysteries of KD. As years have passed, new generations have joined the pioneering efforts of the first generation of KD leaders. IKDS can no longer afford to remain a 3-day event followed by a 3-year long eclipse. KD has clearly become a worldwide issue, and the influx of science has become the harvest of a wide range of disciplines, from climate science to epidemiology to proteomics to artificial intelligence, just to name a few, emerging from a multitude of nations. After 40 years of successful advances being presented at IKDS, it is time for IKDS to branch out, and for the teachings of IKDS to reach deep into the corners of the world where timely diagnosis and providing basic initial therapy with intravenous immunoglobulin are still problematic. IKDS, from a scientific Symposium, has to become a scientific Society. The transformation we envisioned is based on redefining the "S" in the IKDS acronym, from a *Symposium* or a forum for scientific exchange and knowledge sharing, to a *Summit* where decisions are made and the future is planned, to a *Scholastic* where a learning track is constructed with a plan of a teaching curriculum reaching out to new generations of investigators, early career physicians, and primary care health care providers, and finally to a *Society* with bridges with and between existing KD networks, including patient advocacy groups worldwide. The 14th IKDS was successful in bringing this grand idea to the table. Putting together a new society is a major undertaking with stepwise objectives (Fig. 2) to achieve the vision of organizing and governing a collaborative structure for scientists and health care professionals working in the field of KD. With the guidance of past presidents of the previous IKDS meetings, we have initiated a working group of ambassadors with the following vision: (1) inquire about the needs and the perceptions outside of the common circles of KD leadership (senior researchers, seniors advocates, and past presidents) among various community groups and nations, (2) spread information about IKDS conferences and KD research activities where information may be missing, and (3) help encourage both new and established members of the KD community become champions for change. These will be the first steps towards creating a KD academy that will work towards establishing an international society for KD.

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References

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugi*. 1967;16:178–222 [in Japanese].
2. Lin YT, Manlhiot C, Ching JC, et al. Repeated systematic surveillance of Kawasaki disease in Ontario from 1995 to 2006. *Pediatr Int*. 2010;52:699–706.
3. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics*. 2003;112(Pt 1):495–501.
4. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child*. 2015;100:1084–1088.
5. Lin MT, Wu MH. The global epidemiology of Kawasaki disease: review and future perspectives. *Glob Cardiol Sci Pract*. 2017;2017, e201720.
6. Santos MO, Gonçalves LC, Silva PAN, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. *J Pediatr (Rio J)*. 2022;98:338–349.
7. Noval Rivas M, Arditi M. Kawasaki disease and multisystem inflammatory syndrome in children: common inflammatory pathways of two distinct diseases. *Rheum Dis Clin North Am*. 2023;49:647–659.
8. McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. *N Engl J Med*. 2021;385:11–22.
9. ikds.org. International Guidelines of KD. Available at: https://www.ikds.org/copy-of-societies. Accessed September 26, 2024.
10. ikds.org. Foundations. Available at: https://www.ikds.org/copy-of-collaborators. Accessed September 26, 2024.
11. Piram M. Epidemiology of Kawasaki disease in Europe. *Front Pediatr*. 2021;9:673554.
12. Elakabawi K, Lin J, Jiao F, Guo N, Yuan Z. Kawasaki disease: global burden and genetic background. *Cardiol Res*. 2020;11:9–14.
13. Dahdah N, Kung SC, Friedman KG, et al. Falling Through the Cracks: the current gap in the health care transition of patients with Kawasaki disease: a scientific statement from the American Heart Association. *J Am Heart Assoc*. 2021;10:e023310.
14. Denby KJ, Clark DE, Markham LW. Management of Kawasaki disease in adults. *Heart*. 2017;103:1760–1769.
15. Peter E, Fraison JB, Harbaoui B, et al. Cardiovascular outcome in adult-onset Kawasaki disease. *Autoimmun Rev*. 2021;20:102886.
16. Gordon JB, Burns JC. Management of sequelae of Kawasaki disease in adults. *Glob Cardiol Sci Pract*. 2017;2017:e201731.
17. Lam JY, Shimizu C, Tremoulet AH, et al. A machine-learning algorithm for diagnosis of multisystem inflammatory syndrome in children and Kawasaki disease in the USA: a retrospective model development and validation study. *Lancet Digit Health*. 2022;4:e717–e726.

18. Barman P, Pilania RK, Cv G, et al. Treatment intensification in Kawasaki disease—current perspectives. *Expert Rev Clin Immunol*. 2024;20:1179–1191.

19. Dietz SM, van Stijn D, Burgner D, et al. Dissecting Kawasaki disease: a state-of-the-art review. *Eur J Pediatr*. 2017;176:995–1009.

20. NIH. Kawasaki disease; 2024. Available at: https://rarediseases.info.nih.gov/diseases/6816/kawasaki-disease. Accessed September 26, 2024.

21. NORD. Kawasaki disease; 2009. Available at: https://rarediseases.org/rare-diseases/kawasaki-disease/. Accessed September 26, 2024.

22. Huang SK, Lin MT, Chen HC, et al. Epidemiology of Kawasaki disease: prevalence from national database and future trends projection by system dynamics modeling. *J Pediatr*. 2013;163:126–131.e1.

23. Makino N, Nakamura Y, Yashiro M, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016. *Pediatr Int*. 2019;61:397–403.

24. Nakamura Y, Yashiro M, Yamashita M, et al. Cumulative incidence of Kawasaki disease in Japan. *Pediatr Int*. 2018;60:19–22.

25. Dionne A, Bakloul M, Manlhiot C, et al. Coronary artery bypass grafting and percutaneous coronary intervention after Kawasaki disease: the pediatric canadian series. *Pediatr Cardiol*. 2017;38:36–43.

26. Brogan P, Burns JC, Cornish J, et al. Lifetime cardiovascular management of patients with previous Kawasaki disease. *Heart*. 2020;106:411–420.

27. Watanabe M, Fukazawa R, Kamisago M, et al. Prognosis of coronary artery bypass grafting in preschool-aged patients with myocardial ischemia due to giant aneurysm of Kawasaki disease. *J Clin Med*. 2022;11:1421.

28. Warisawa T, Cook CM, Kawase Y, et al. Physiology-guided PCI versus CABG for left main coronary artery disease: insights from the DEFINE-LM registry. *Cardiovasc Interv Ther*. 2023;38:287–298.

29. Channon-Wells S, Vito O, McArdle AJ, et al. Immunoglobulin, glucocorticoid, or combination therapy for multisystem inflammatory syndrome in children: a propensity-weighted cohort study. *Lancet Rheumatol*. 2023;5:e184–e199.