The Epidemiology and Management of Kawasaki Disease in Australia

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Declaration

The work presented in this thesis is, to the best of my knowledge, original except as acknowledged in the text. I hereby declare that appropriate ethical review and approval was sought for this work and that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Signature: ..... Date: .....

Works Arising from this Thesis

Original Articles in Print

1. **Lucas R**, Dennington P, Wood E, Dionne A, Ferranti SD, Newburger JW, *et al*. Variation in the management of Kawasaki disease in Australia and New Zealand: A survey of paediatricians. *J Paediatr Child Health*. 2020 Dec 9;jpc.15290.

2. **Lucas R**, Dennington P, Wood E, Murray KJ, Cheng A, Burgner D, *et al*. Epidemiology of Kawasaki disease in Australia using two nationally complete datasets. *J Paediatr Child Health*. 2021 Oct 30;jpc.15816.

3. Cardenas-Brown C, **Lucas RD**, Buttery J, Britton PN, Wood N, Singh-Grewal D, *et al*. Live vaccines following intravenous immunoglobulin for Kawasaki disease: Are we vaccinating appropriately? *J Paediatrics Child Health*. 2023 Sep 4;jpc.16484.

Presentations

1. Kawasaki disease in Australia: epidemiology, management, outcomes. *Rheumatology East Coast Journal Club* (oral presentation). 2021.

2. Prospective surveillance of Kawasaki disease in Australia: diagnosis, management, and outcomes. *The 13th International Kawasaki Disease Symposium* (oral presentation). 2021.

3. The Epidemiology & Management of Kawasaki disease in Australia. *Grand Rounds — Sydney Children's Hospital, Randwick* (oral presentation). 2019.

4. Management of Kawasaki disease in Australia and New Zealand: a survey of clinician practices. *Annual Scientific Meeting — Australasian Society for Infectious Diseases* (poster presentation). 2019.

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The study presented in Chapter 3 represents an analysis of local responses to an international survey on Kawasaki disease (KD) diagnosis and management. I am indebted to the researchers who planned and undertook that survey: Dr Audrey Dionne, Associate Professor Sarah de Ferranti, Professor Jane Newburger, and Professor Nagib Dahdah. Thank you for graciously allowing me to start my research career on your dataset.

The study presented in Chapter 4 (estimating the incidence of KD in Australia using two datasets) was only possible thanks to the Australian Red Cross Lifeblood, who permitted me access to their dataset on intravenous immunoglobulin (IVIG). I would particularly like to thank Dr Peta Dennington, who held my hand as I analysed those data. Her depth of knowledge on the history and processes of immunoglobulin product distribution were absolutely critical to accurately interpreting the data. I am also grateful to Professor Erica Wood for her input and assistance.

The study presented in Chapter 5 (a retrospective audit of immunisation with live vaccines in children treated for KD with IVIG) represents the actualisation of an idea that had originally been conceived as an honours thesis by Professor Jim Buttery, Dr Peter Gowdie, and Professor David Burgner. transfusion database. That thesis, prepared by Dr Joel Le Couteur of Monash University, prepared the foundations of this work. I am grateful to everyone who contributed to that work for permitting me to take it further. The study required access to the Australian Immunisation Register (AIR); I am grateful to Professor Nick Wood, who not only facilitated access to AIR, but provided

invaluable insights that informed the final work. Finally, I am grateful to my co-author Dr Casandra Cardenas-Brown; much of the leg work for this project was hers, and her assistance in preparing the manuscript was greatly appreciated.

The study presented in Chapter 6 (prospective surveillance of KD in Australia) is the largest undertaking in this thesis by far. The project was only possible thanks to the commitment of the many research staff who comprise the Paediatric Active Enhanced Disease Surveillance (PAEDS) network. I am thankful to Professor Kristine Macartney, Professor Nick Wood, Dr Phil Britton, and the PAEDS investigators for giving me the opportunity to undertake this research using the PAEDS network. Having previously walked a similar path, Phil's sage advice helped me avoid innumerable mistakes — I am in his debt. I am also grateful to the PAEDS surveillance nurses, whose commitment to quality, even during a pandemic, is truly inspirational. I would particularly like to thank Laura Rost, Jocelynne McRae, Kathryn Meredith, Gemma Saravanos, and Nicole Dinsmore; your commitment and friendship are greatly valued. Finally, I am grateful to the children and families afflicted by KD. Their fear, pain, and suffering lie behind the statistics and charts presented herein.

The postscript to this thesis was a (ill-informed) hobby horse; it represents my first attempts to articulate deep misgivings about the Kawasaki Disease Paradigm as currently conceived. That my supervisors allowed me such indulgence (the outcome of which was an overdue thesis submission) is a testament to their patience and grace. I am grateful to Professor Werner Ceusters, of The State University of New York. His published works on health informatics, and his gracious personal correspondence, helped me develop the cognitive apparatus necessary for this critique.

It has taken me far longer to complete this thesis than I intended — over five years. During those years I lost my father, Dr Graeme Lucas. Dad was the reason I went into medicine, and paediatrics. He was a man of integrity, humanity, and grace — to me he was a giant. I dedicate this thesis to him.

The loss of my Dad was a difficult time, yet throughout it my mother Christine gave me her unwavering support; I am deeply grateful. In my relative absence my brother Brad took on many responsibilities for the family; he has my deepest respect and thanks.

The greatest burden over these years was born not by me, but by my family: my wife Madeleine and son Arthur, both of whom I love beyond words. Many mornings I left the house before 5AM in search of a quiet place to write before starting my clinical work; the externality of that practice was that Maddie

functioned as a single parent, and Arthur started the day without seeing his dad. As I move forward from this endeavour, I dedicate myself to them.

Abstract

Background

Kawasaki disease (KD) is a syndrome of systemic inflammation with the potential to cause life-threatening aneurysms of the coronary arteries. It almost exclusively affects young children. The current epidemiology, management, and outcomes of KD in Australia has had little attention. In this doctoral work I sought to contribute to our understanding of this important condition, particularly with regard to Australian children.

Survey on the Management of KD

Firstly, I analysed the Australian and New Zealand responses to an international survey on the management of KD. I identified considerable variation in reported practice on a number of issues; notably, the use of aspirin in the acute phase of the disease, and the diagnosis and management of intravenous immunoglobulin (IVIG) resistant KD.

Epidemiology of KD in Australia

Secondly, I analysed two independent national datasets to retrospectively estimate the incidence of KD in Australia. By determining the hospitalisation rate and IVIG-treatment rate I estimated the incidence to be about 14 per 100,000 children under the age of 5 between 2007 and 2015. I also showed that the hospitalisation rate nationally had increased on average 3.5% annually between 1993 and 2018, with significant changes in the age distribution over that period. Finally, by analysing records of IVIG treatment I reported the first evidence of (modest) seasonal variation in KD rates in Australia.

Live Vaccines After IVIG for KD

Thirdly, I undertook a retrospective audit of immunisation practices among children previously treated with IVIG for KD. Due to the potential for IVIG to interfere with the body's response to live vaccines, Australian immunisation guidelines recommend that live vaccines be postponed for 11 months after IVIG for KD; however, little is known about real-world practice. I identified that most children who received IVIG in the 11 months prior to a scheduled live vaccine did not have that immunisation postponed. This suggests that some children who are appropriately treated for KD may subsequently be ineffectively immunised and highlights the need for iterative improvement of the public health infrastructure that prevents the re-emergence of vaccine-preventable diseases.

Prospective Surveillance of KD in Australia

Finally, in collaboration with the Paediatric Active Enhanced Disease Surveillance (PAEDS) network, I undertook a large multicentre prospective surveillance study of KD in Australia. My analysis of that cohort confirmed several of the findings from the survey, such as the preference of Australian clinicians for low-dose aspirin from the time of diagnosis, and the considerable variability around how IVIG resistance is diagnosed and managed. Importantly, I observed that a significant subset of children diagnosed with, and treated for, KD do not meet the diagnostic criteria outlined in the 2017 statement by the American Heart Association.

Conclusions

This work has contributed significantly to the understanding of KD's epidemiology, management, and outcomes in Australia. I have shown that the incidence of the condition is increasing, and the clinical picture is changing. I identified important areas of practice variation and highlighted the need for international collaboration around agreed definitions (such as for IVIG resistance). I uncovered vulnerabilities in the immunisation programme, which is poorly equipped to accommodate children with KD. Finally, I have played a central role in establishing an important resource for future resource: prospective surveillance of KD in Australia continues, with well over 700 cases recruited so far. It is hoped that this work will be of benefit to the researchers, clinicians, patients, and families affected by KD now, and into the future.

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Foreword

Kawasaki disease (KD) is one of the leading causes of acquired heart disease worldwide[1]; it is an acquired inflammatory condition that typically affects children under the age of five years.[2] KD is a systemic vasculitis of arteries, but particularly affects the coronary arteries.[3–6] Affected coronary arteries can range from mild dilatation to giant aneurysms—with or without subsequent stenosis, thrombosis, or rupture.[7,8] Prior to the introduction of effective treatment, around 15–35% of children afflicted with KD developed aneurysms of their coronary arteries[9–11]; 1–2% died.[12,13]

The etiology of KD remains unknown despite over fifty years of intense investigation.[14–17] In the absence of a known cause, efforts to develop a diagnostic test have been hampered by poor sensitivity and specificity.[18–23] The diagnosis of KD therefore remains clinical—relying on the observation of a minimum set of cardinal clinical features in the context of fever.[2,24,25] These criteria are derived from the first case series of KD by Dr Tomisaku Kawasaki and comprise fever, non-purulent conjunctivitis, inflammation of the mucosal membranes, cervical lymphadenopathy, polymorphous rash, and acral oedema.[26] Initially intended as an epidemiological case definition of KD, these criteria now form the central diagnostic tool for the condition.[2,24,25] The observation of cardiac sequelae in children who did not fulfil these strict criteria (for what is now called "Complete KD") has lead the recognition of "Incomplete KD", diagnosed according to an expanded set of clinical and laboratory criteria.[27–29] Epidemiological and interventional studies vary as to which definition they use for KD.

KD was first reported in Australia in in 1976.[30] Subsequent studies suggested a rising incidence of KD in Australia: The Australian Paediatric Surveillance Unit surveyed paediatricians between1993 and 1995, producing a more robust national incidence estimate of 3.7 per 100,000.[31] Finally, Saundankar *et al* undertook a 30-year retrospective chart review of KD cases in Western Australia based on discharge diagnosis. They showed that the annual incidence increased each decade during that period: from 2.8 per 100,000 children under 5 between 1979 and 1989 to 9.3 per 100,000 children under 5 between 1999 and 2009.[32] This phenomenon has been widely reported globally, although its drivers remain unclear.[33–35]

The management of KD rests on the use of intravenous immunoglobulin (IVIG)—a blood product derived from donor blood plasma.[2,24,36] IVIG is the only intervention proven to reduce the incidence of coronary artery aneurysms,[37] and there is a general consensus that children with KD should receive IVIG at a dose of 2 g/kg as soon as possible.[2,24,36] There are a number of important considerations that are relevant to the use of IVIG in the management of KD. Adverse clinical events related to IVIG are rare but do

occur.[38,39] IVIG has been shown to interfere with seroconversion in response to immunisation with live vaccines—an issue of particular relevance to children with KD, who are often at the age when these vaccines are recommended.[40,41] Another issue is that of IVIG resistant KD: while IVIG is largely effective in quelling the inflammation of KD, up to a quarter of children may require additional doses for this effect.[2,42,43] There is currently a lack of consensus around how the diagnosis of IVIG resistant KD is made, and how it ought to be managed.[44] Finally, as a blood product IVIG is a valuable resource with limited supply. In Australia, IVIG for the treatment of KD is provided without cost to patients by the Australian Red Cross Lifeblood through a funding agreement between the Commonwealth Government and the various States and Territories.[45] The use of publicly-funded IVIG is governed by strict criteria and overseen by a dedicated statutory authority—the National Blood Authority.[46] There is a strong interest in understanding changing IVIG needs for resource management and planning.[47]

Aspirin is also commonly used in the management of KD, however there is controversy around its function and dosing.[48–51] Aspirin has traditionally been thought to fulfil two roles in KD: suppression of inflammation (largely mediated by COX-2 inhibition at high aspirin doses) and prevention of thrombosis (via COX-1 inhibition at low aspirin doses).[48] Most clinical practice guidelines recommend that children with KD receive aspirin in a higher dosing range* during the febrile phase of the disease, after which low-dose aspirin is continued as thromboprophylaxis.[2,36,52] Australian guidelines are notable for only recommending low-dose aspirin for children with KD.[24,53] Other agents sometimes used in the acute phase of KD include corticosteroids,[54] biologic agents (such as the anti-TNF-α drug infliximab[55]), and immunosuppressive drugs[56]. The role of these agents is a topic of ongoing research.[57]

This thesis aims to expand upon our understanding of KD in Australia. The work is presented in three parts. Part One includes two narrative reviews that expand on the brief summary given above. Part Two (the main body of the thesis) includes four original papers (two published manuscripts and two submitted manuscripts), each investigating different aspects of the epidemiology and management of KD in Australia. Part Three includes a concluding chapter and a reflective essay. Finally, three published manuscripts that arose from (but were not a part of) this doctoral work are presented in the Appendices. The works contained in the appendices are associated with the description and surveillance of Paediatric Inflammatory Multisystem Syndrome—Temporally Associated with SARS-CoV-2 in Australia which

* Either moderate-dose aspirin (30–50 mg/kg/day) or high-dose aspirin (80–100 mg/kg/day).

occurred during the period of KD surveillance and provided an exciting opportunity to be part of ground-breaking work in this area in Australia.

The following paragraphs outline the contribution of each chapter to the thesis:

Part One

Chapter One presents a short review summarising the current literature regarding the global epidemiology of KD.

Chapter Two presents a longer review of the management of KD. Written in five parts, this comprehensive and critical review addresses the roles of IVIG, aspirin, corticosteroids, and biologic agents in the management of acute KD, and discusses the issue of IVIG resistance.

Part Two

Chapter Three presents the results of a survey of Australian and New Zealand practitioners on a range of issues relevant to the diagnosis and management of KD. The survey found that there was broad consensus around the use of IVIG but revealed considerable disagreement with regards to aspirin dosing and the diagnosis of IVIG resistance. This study has been published in *The Journal of Paediatrics and Child Health* and was presented as a poster at the 2019 Annual Scientific Meeting of The Australasian Society for Infectious Disease. Both the published manuscript and supplementary results are included in this thesis.

Chapter Four presents the results of an Australia-wide epidemiological study that combined two large datasets to estimate the incidence of KD in Australia. This analysis demonstrated a steady rise in the rate of hospitalisation for KD over 25 years while confirming that the demographic picture of the disease in Australia closely resembles that described elsewhere. This study has been published in *The Journal of Paediatrics and Child Health*.

Chapter Five presents the results of a multi-centre retrospective study of the use of live vaccines in children who had received IVIG for the treatment of KD. This study found that Australian clinicians struggled to comply with national guidelines that recommended postponing live vaccines for a period of 11 months after IVIG for KD. This study has been submitted for publication in *The Journal of Paediatrics and Child Health* and will be presented at the 2023 Annual Scientific Meeting of The Australian Rheumatological Association.

Chapter Six presents the results of a large multi-centre prospective surveillance study of KD: the Paediatric Active Enhanced Surveillance—

Kawasaki Disease (PAEDS–KD) study. This study revealed some of the highest rates of IVIG retreatment in the world and sought to understand some of the drivers of this phenomenon. Representing the largest study of its kind in the Southern Hemisphere, the PAEDS–KD study—which continues to enrol participants—promises to provide an invaluable insight into the demographics, treatment, and outcomes of KD in Australia into the future. This analysis has been prepared for submission to *The Lancet Regional Health—Western Pacific* and was presented as an oral presentation at the 2021 International Kawasaki Disease Symposium.

Part Three

Chapter Seven presents the Conclusion, summarising and synthesising the key original insights into the epidemiology and management of KD that have emerged from this doctoral research. Suggestions for future research priorities will also be presented.

Chapter Eight is a reflective essay presented as a Postscript. In this essay I reflect on the Kawasaki Disease paradigm—its evolution and limitations. I conclude with tentative thoughts on an alternative paradigm, and how this might better serve future research.

Appendix

The appendix presents an early narrative review on the then-emerging entity of Paediatric Inflammatory Multisystem Syndrome—Temporally Associated with SARS-CoV-2 (PIMS-TS). This work, published in *The Journal of Paediatrics and Child Health* in early 2020, sought to summarise what was known about the condition at that time, comparing and contrasting with KD, KD shock syndrome, and toxic shock syndrome.

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Chapter 1:
The Epidemiology of Kawasaki Disease

Kawasaki published the first case series of the condition he termed muco-cutaneous lymph node syndrome in 1967; the series included fifty patients from the Tokyo area.[1] Since that publication Kawasaki disease (KD) has been reported in populations throughout the world,[2–5] however the incident rate remains highest[*] in Japan.[7]

Incidence

Methodological Considerations

Incidence is defined as the number of new cases of a disease divided by the population at risk over a set interval of time.[8] The *population at risk* depends on the nature of the disease: the incidence of endometrial cancer in a given year would be calculated as:

$$\frac{Cases\ of\ endometrial\ cancer\ in\ study\ year}{People\ with\ a\ uterus\ in\ the\ population\ that\ year}$$

Such that males and women who had undergone a hysterectomy are excluded from the analysis. KD largely occurs in children <5 years of age, and so the population at risk is usually defined according to age—most frequently as the number of cases of KD in children <5 years[†] per 100,000 children <5 years of age,[7,10–12] as follows:

$$\frac{KD\ cases < 5\ years\ of\ age\ in\ study\ year}{Children < 5\ years\ of\ age\ in\ study\ year} \times 100{,}000$$

Incidence in other age brackets is also frequently reported, including <1 year of age, 5–9 years of age, and 10–14 years of age.[10‡]

Estimates of the incidence of KD have been published from populations around the world (**Table 1.1**). Various approaches to case ascertainment have been used, including intermittent hospital or practitioner surveys,[7,11,14–17] audits of administrative data (such as discharge diagnosis codes or insurance claims data),[18–20] and prospective surveillance.[21,22] Prospective studies, and

[*] Japan's high incidence of KD is matched only by that of Hawai'i.[6]

[†] While the numerator almost always represents has the same age brackets as the denominator, this is not always clearly specified in the *Methods* sections of epidemiological papers. As standard convention[8] it can usually be assumed, however not always: Du *et al* (2007) appear to have used the total case number for the numerator in their calculation of KD incidence in Beijing.[9]

[‡] This is often dictated by the availability of population data, determined by the reporting practices of national censuses. Other age brackets have been used: Anderson and Hurwitz reported KD incidence in children ≤8 years of age.[13]

some retrospective studies with access to clinical information, seek to apply a strict epidemiological case definition—such as those published by the Japan Kawasaki Disease Research Committee (JKDRC),[23,24] the Centers for Disease Control and Prevention (CDC),[25] and the American Heart Association (AHA).[26–28] The main strengths of these studies are specificity and comparability: since each case is reviewed individually there is opportunity to critically appraise the diagnosis according to standardised criteria—criteria that can be applied by other researchers for comparison between populations or in one population over time.[29] An issue can arise when there are differences between case definitions (such as between those published in North America and Japan[*]) or when case definitions change over time. While the former has been a relatively minor issue (the differences between North American and Japanese definitions being subtle), the latter has been significant. The recognition that the epidemiological case definition lacked sensitivity for so-called "incomplete KD" lead to the construction of expanded criteria for enhanced clinical diagnosis.[30,31] This not only complicates comparisons over time, but highlights the systematic under-counting of cases using this approach. These kinds of studies are also limited by the labour required to review case notes; for this reason, they have tended to be limited in scope both geographically and temporally.

Another approach has been to estimate incidence by leveraging large administrative datasets without access to individual patient clinical information, typically from hospital discharge codes (such as the International Classification of Disease [ICD] codes ICD-9 446.1 or ICD-10 M30.3)[32–34] or from insurance claims data.[35] In these studies the rate of disease occurrence (i.e. incidence) is assumed to be similar to another variable, such as the hospitalisation rate. These methods benefit from access to comparatively large datasets, the analysis of which is relatively cheap in terms of research time and capital.[29] Unfortunately, the core assumption—that one hospitalisation equals one case (and *vice versa*)—is frequently untrue. At least 10% of KD cases require readmission during the disease episode,[20,36,37] however these repeated admissions can be difficult (or impossible) to differentiate from the index admission in large datasets.[†] Misdiagnoses and data entry errors can also

[*] North American case definitions for KD have required the presence of fever for at least 5 days (as a *sine qua non* for the diagnosis) plus at least 4 out of 5 cardinal clinical features (polymorphous exanthem, conjunctival injection, oral mucocutaneous inflammation, cervical lymphadenopathy, and acral changes such as palmar/solar induration or periungual desquamation).[26,27] Japanese case definitions have differed by treating fever as 1 of 6 cardinal clinical features, of which at least 5 must be present for the diagnosis to be made.[23,24]

[†] Large datasets of discharge diagnoses are usually de-identified and often presented as aggregated (rather than individualised) data. This is true of Australian hospitalisation data contained in the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database,[38] the use of which was central to the work presented in Chapter Four of this thesis.

undermine the core assumption.[29] All of these issues have resulted in incidence estimates that are not easily compared.[12,39] Consequently, caution is advised when interpreting individual estimates.

Incidence Estimates

Estimates of KD incidence from around the world have been highly heterogenous (**Table 1.1**). The most recent incidence estimate for KD in Japan was 359 per 100,000 children <5 per year[40]; this compares with a rate of 196.9 per 100,000 children <5 in Korea[16] and 60 per 100,000 children <5 in Taiwan (**Figure 1.1**).[19] Outside of east-Asia the incident rate is much lower: in Canada the incidence was 19.6 per 100,000 children <5 (**Figure 1.2**),[39] and in Australia was 9.3 per 100,000 children <5 per year (**Figure 1.3**).[10] European countries report some of the lowest rates of KD: 4.6 per 100,000 children <5 in the United Kingdom,[11] 11.7* per 100,000 children <5 in Spain,[42] and 8.4 per 100,000 children <5 in Switzerland (**Figure 1.4**).[22]

There is evidence that the incidence of KD is increasing, however the rate of increase differs markedly by region. Data from the 22 bi-annual Japanese surveillance studies demonstrate that the current annual incidence of KD in Japan has exceeded the highest peak incidence of any of the previous epidemics (**Figure 1.1**).[15] Indeed, Burns *et al* found that the incidence had increased by 90% over a fourteen-year period that did not include any discrete epidemics.[43] Evidence also exists for an increasing incidence in Canada, India, and England.[44–46]

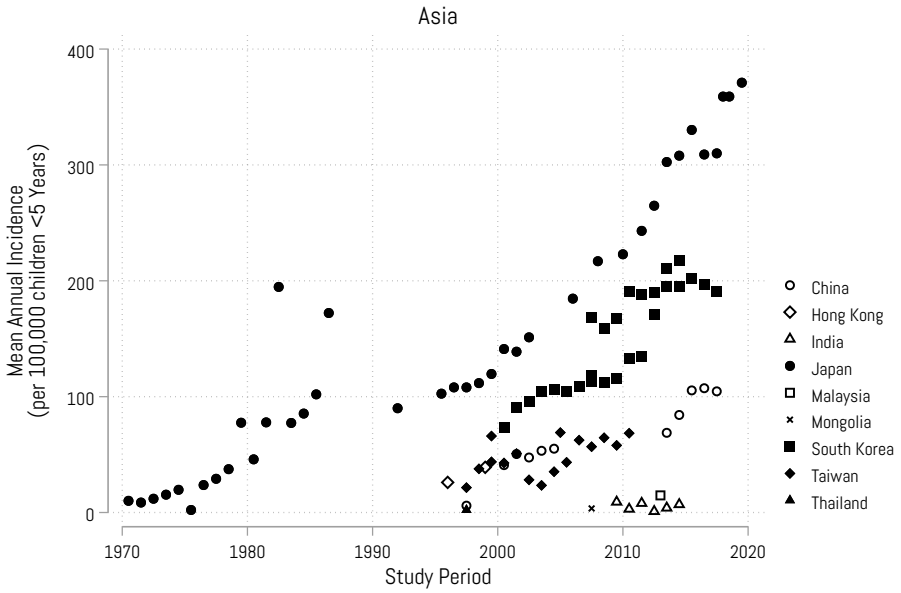

Figure 1.1: Published estimates of Kawasaki disease incidence from Asia.

What appear as point estimates are, in fact, estimates from year- or multi-year-long studies that have been annualised with the marker situated at the midpoint of the study. All estimates are taken from studies listed in **Table 1.1**.

* For methodological reasons this number may be an overestimate.[41]

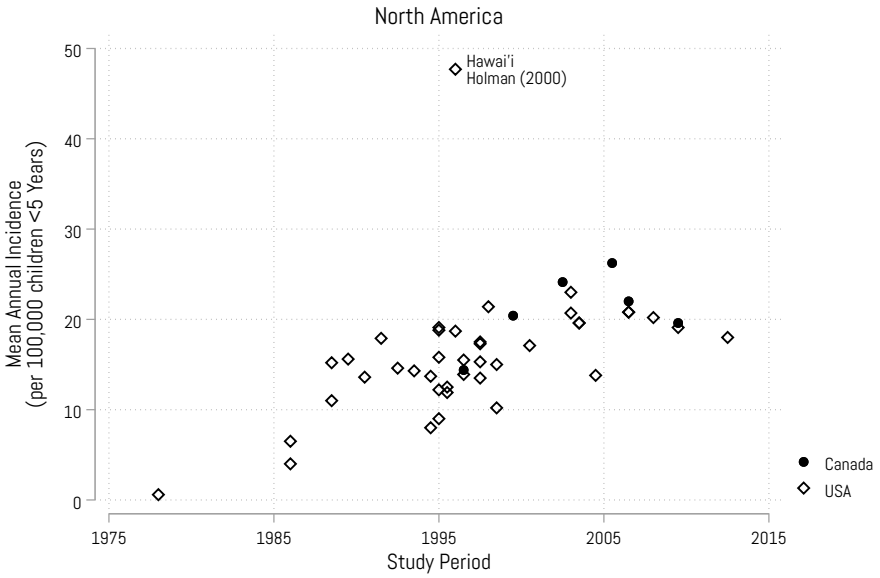

Figure 1.2: Published estimates of Kawasaki disease incidence from North America.

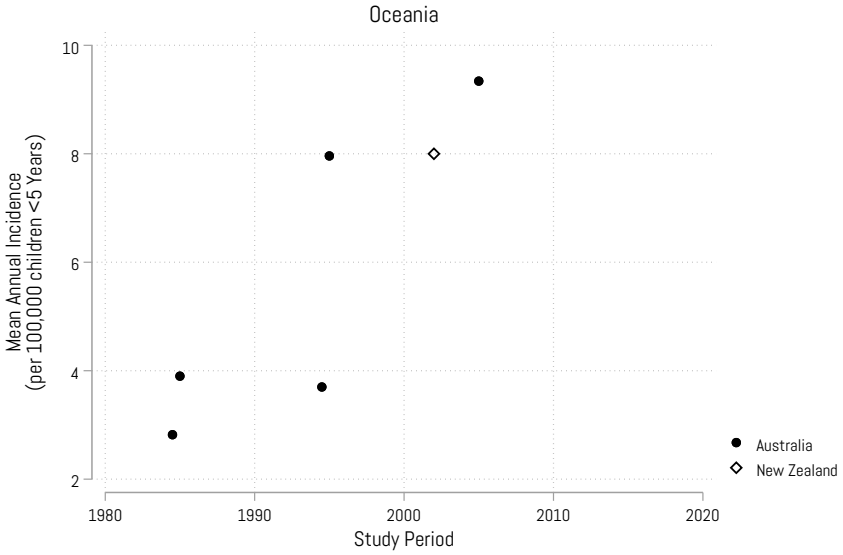

Figure 1.3: Published estimates of Kawasaki disease incidence from Oceania.

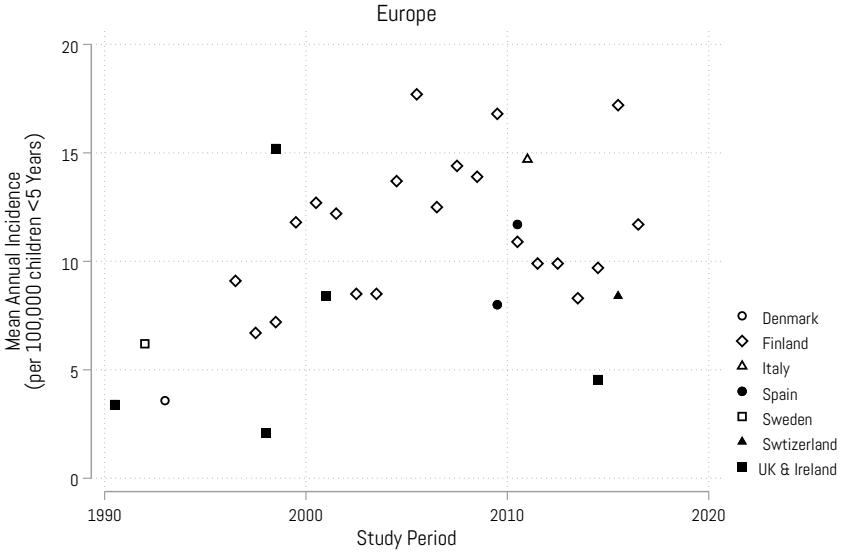

Figure 1.4: Published estimates of Kawasaki disease incidence from Europe.

Clustering and Seasonality

Epidemics of KD have been observed on the large scale, at least three large epidemics identified in the Japanese surveillance data: one in 1979, one in 1982, and another in 1986.[15] Clustering of cases on a small scale is much more difficult to identify and prove; Burns *et al* compared a retrospective Japanese dataset of KD cases against a simulation of random incident cases using a Monte Carlo experiment; they were able to provide evidence of temporal clustering, however this temporal clustering was not mirrored as geographical clustering.[14,15,43] Fujita *et al* undertook a study of KD recurrence within families and found evidence of clustering, with siblings of an index case having a significantly increased risk of KD within the first 10 days.[47]

There does appear to be some seasonal variation in KD incidence, however the prominent season differs by location. Data from 22 bi-annual Japanese sentinel surveillance studies demonstrate a regular bimodal pattern of seasonality: there is a major peak in January (with lowest annual temperatures), with a minor peak in June/July (the months with the highest annual precipitation.[15] Burns *et al* undertook a sophisticated analysis of all published epidemiologic data on KD from 25 countries; they concluded that there was significant seasonality in the Northern Hemisphere extra-tropical regions, again having a zenith in the Northern winter (from January to March).[48] They were unable to find strong evidence for seasonal variation in the tropical regions or in the Southern Hemisphere, though this could be attributed to a paucity of published longitudinal data from these regions.

Age and Sex

The age distribution is characteristic. There is a monomodal peak in young childhood, with 85% of cases occurring in children under the age of five; incidence over this age drops precipitously[49]; conversely, the disease is uncommon under the age of 3 months.[50]

Studies have repeatedly demonstrated a male predominance in KD incidence, with the male to female ratio usually reported around 1.5:1.[17,34,51,52]

Epidemiology and Aetiology

While the cause of KD remains unclear, epidemiological observations have provided some intriguing clues. Differences in incidence rates have been cited to propose environmental agents as a cause for KD—implicating atmospheric dispersion of an agent from China as a possible reason for the high rates of disease in Japan and low rates in Europe.[53] Others have suggested an infectious cause: the rapidly-increasing incidence in East Asia has been attributed to the introduction of a novel pathogen into a naïve population.[6] The significance of the age distribution has also been highlighted. Rowley noted that the peak age

for KD matches that of common childhood infections, and suggested that KD is caused by an infectious agent: ubiquitous in early childhood, with immunity arising in most people, and with newborns protected by passively-acquired maternal antibodies.[50,54,55] Others have focussed on the apparent seasonal variation in KD incidence: such variation is commonly observed with respiratory pathogens, again leading to the suggestion that KD is (or is triggered by) an infectious disease.[43,56–58]

It should be noted that apparent "clues" from epidemiological studies can mislead as well as inform. Findings from a case-control study during an apparent outbreak of KD in Colorado in 1982 seemed to implicate exposure to rug shampoo as a trigger for the disease.[59] Similar observations by clinicians in New York seemed to support an association,[60] however subsequent studies found no evidence of an effect.[61] Rug shampoo is no longer thought to have an association with KD.[62,63] Similar "associations" between KD and a range of agents have been proposed and subsequently debunked, including childhood vaccines,[64–67] coronavirus NL63,[68,69] rotavirus,[57] adenovirus,[70] and—most recently—SARS-CoV-2.[71] Caution is again recommended when interpreting the results of epidemiological studies.

Kawasaki Disease in Australia

The first known case of KD in Australia was reported in 1976: a 5-month-old boy from Adelaide who died after febrile illness lasting 2 weeks and with all of the cardinal clinical features of KD.[72] The first Australian epidemiologic study was reported in 1993; also based in Adelaide, it presented a series of 51 patients and estimated the annual incidence for children under 5 years to be 3.9 per 100,000.[73]

Subsequent studies suggested a rising incidence of KD in Australia: The Australian Paediatric Surveillance Unit surveyed paediatricians between1993 and 1995, producing a more robust national incidence estimate of 3.7 per 100,000.[17] Finally, Saundankar *et al* undertook a 30-year retrospective chart review of KD cases in Western Australia based on discharge diagnosis. They showed that the annual incidence increased each decade during that period: from 2.82 per 100,000 children under 5 between 1979 and 1989 to 9.34 per 100,000 children under 5 between 1999 and 2009.[10]

There has been comparatively little research on the epidemiology of KD in Australia, with the only nation-wide survey now 30 years old. Given the apparent increase in incidence described in previous studies, and the implications thereof for health resource planning, there is a clear need to update the incidence estimate at a national level.

Table 1.1: Published Estimates of Kawasaki Disease Incidence

Study Name	Region	Country	Period	Cases	Incidence	Notes
Bell (1983)[74]	North America	USA	1976–80	593	0.59	Methodology is difficult to categorise as "...cases come to the attention of the CDC through a variety of mechanisms." Case definition was according to Bell *et al.*[75]
Yanagawa (1988)[14]	Asia	Japan	1964–86	83,857	Multiple	Retrospective surveillance through hospital surveys. This paper summarised previous surveys and listed the estimated yearly incidence from 1964 to 1986. Estimates from 1970 inwards are included in graphs.
Windsor (1991)[76]	North America	USA (Wisconsin)	1982–89	160	4.0	Prospective surveillance through case reporting to the Wisconsin Division of Health. Case definition was according to the CDC.[77]
Smith (1993)[73]	Oceania	Australia (Adelaide)	1979–90	55	3.9	Retrospective case review at four major hospitals in Adelaide. Case definition was according to Shulman *et al.*[26]
Salo (1993)[78]	Europe	Finland	1982–92	229	3.1–7.2	Prospective surveillance through case reporting. Case definition according to the JKDRC.[23] As only a range of incidence values was given, these data are not included in graphs.
Dhillon (1993)[51]	Europe	UK	1990	163	3.4	Prospective surveillance through case reporting to the BPSU. Case definition was according to Shulman *et al.*[26]
Yanagawa (1995)[79]	Asia	Japan	1991–92	11,221	90	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Schiller (1995)[80]	Europe	Sweden	1991–92	99	6.2	Prospective surveillance through case reporting to the Swedish Kawasaki Study. Case definition according to the AHA.[81]
Davis (1995)[82]	North America	USA (Washington)	1985–89	110	6.5 (1985–86) 15.2 (1987–89)	Retrospective audit of hospital admissions data (1985–86) and prospective surveillance through case reporting (1987–89). Case definition according to the CDC.[25]
Royle (1998)[17]	Oceania	Australia	1994	139	3.7	Prospective surveillance via case reporting to the APSU.
Yanagawa (1998)[83]	Asia	Japan	1995–96	12,531	102.6 (1995) 108.0 (1996)	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]

Continued...

Table 1.1 continued...

Study Name	Region	Country	Period	Cases	Incidence	Notes
Holman (2000)[32]	North America	USA (Hawai'i and Connecticut)	1987–96 (Connecticut) 1994–97 (Hawai'i)	366 (Connecticut) 175 (Hawai'i)	16.0 (Connecticut) 47.7 (Hawai'i)	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). Only children <5 years old included. No chart review; readmissions not excluded.
Pierre (2000)[84]	Central & South America	Jamaica	1986–89	57	2.7	Retrospective case review at all referral hospitals and regional specialist hospitals. Case definition according to the CDC.[85]
Bronstein (2000)[86]	North America	USA (San Diego County)	1994–98	169	8.0–15.4	Retrospective case review at six hospitals in the county. Case definition according to AHA.[81] Individual yearly estimates for incidence were estimated from a bar chart for inclusion in graphs.
Belay (2000)[33]	North America	USA (West Coast)	1993–96)	234	9.7–18.7	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions were excluded.
Yanagawa (2001)[87]	Asia	Japan	1997–98	12,966	108.8 (1997) 111.7 (1998)	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Chang (2002)[34]	North America	USA (California)	1559–99	2,325	15.3	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions not excluded.
Gardner-Medwin (2002)[88]	Europe	UK (West Midlands)	1996–99	73	2.1	Retrospective case review of cases identified through clinician surveys. Case definition according to the AHA.[81]
Du (2003)[89]	Asia	China (Beijing)	1995–99	537	5.93	Prospective surveillance through case reporting. Case definition not given.
Holman (2003)[90]	North America	USA	1988–97	27,546	11.0–17.9	Weighted estimate of hospitalisation rate using the Nationwide Inpatient Sample, which samples hospital admission at a number of states across the USA. No chart review. Readmissions not excluded.
Belay (2003)[91]	North America	USA	1997–99	7,431	10.2	Weighted estimate of hospitalisation rate using a proprietary health database that samples hospitalisations at participating hospitals across the USA. No chart review. Readmissions not excluded.
Lynch (2003)[92]	Europe	Ireland	1996–2000	265	15.2	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions not excluded.

Continued...

Table 1.1 continued...

Study Name	Region	Country	Period	Cases	Incidence	Notes
Chang (2004)[52]	Asia	Taiwan	1996–2002	7,305	66.0	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions not excluded.
Panamonta (2004)[93]	Asia	Thailand (Central Northeast)	1991–2003	72	2.2	Retrospective case review at three major referral hospitals.
Ng (2005)[94]	Asia	Hong Kong	1994–2000	696	26 (1994–97) 39 (1997–2000)	Retrospective audit of hospital admission records (1994–97) and prospective surveillance through case reporting to the HKKDSG (1997–2000). Case definition according to the AHA.[81]
Yanagawa (2006)[95]	Asia	Japan	1999–2002	32,266	137.7	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23] Yearly estimates are included in graphs.
Heaton (2006)[96]	Oceania	New Zealand	2001–02	49	8.0	Prospective surveillance via case reporting to the NZSU.
Du (2007)[9]	Asia	China (Beijing)	2000–04	1,107	49.4	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). Case reviews conducted by physicians, however case definition not given. It was not clear from this paper that the numerator for the incidence calculation was children <5 years with KD.
Fischer (2007)[97]	Europe	Denmark	1981–2004	360	3.6	Retrospective audit of hospital admission by discharge diagnosis (ICD-8 446.9 or ICD-10 M30.3). No chart reviews. Readmissions were excluded.
Nakamura (2008)[98]	Asia	Japan	2005–06	20,475	184.6	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Huang (2009)[19]	Asia	Taiwan	2003–06	3,877	69	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions not excluded.
MacNeil (2009)[57]	North America	USA (California and New York)	2000–05	n/a	20.7 (California) 23.0 (New York)	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions not excluded.
Harnden (2009)[37][46]	Europe	England	1998–2003	1,228	8.4	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions not excluded.

Continued...

Table 1.1 continued...

Study Name	Region	Country	Period	Cases	Incidence	Notes
Coustasse (2009)[99]	North America	USA (Texas)	2004	247	13.8	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). No chart review; readmissions not excluded.
Nakamura (2010)[100]	Asia	Japan	2007–08	23,337	216.9	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Holman (2010)[20]	North America	USA	1997–2007	n/a	17.1–20.1	Weighted estimate of hospitalisation rate using the Nationwide Inpatient Sample, which samples hospital admission at a number of states across the USA. No chart review. Readmissions not excluded.
Lin (2010)[44]	North America	Canada (Ontario)	1995–2006	2,378	14.4–26.2	Repeated retrospective audit of hospital admissions by discharge diagnosis (ICD-8 446.9 or ICD-10 M30.3). Chart reviews performed. Readmission >7 days after return to baseline were coded as an additional episode of KD.
Park (2011)[101]	Asia	South Korea	2006–08	9,039	113.1	Retrospective surveillance through hospital surveys.
Nakamura (2012)[102]	Asia	Japan	2009–10	23,730	222.9	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Kim (2014)[103]	Asia	South Korea	2009–11	13,013	115.4–134.4	Retrospective surveillance through hospital surveys. Annual estimates presented from 2000 to 2014 were used for graphs.
Saundankar (2014)[10]	Oceania	Australia (Western Australia)	1979–89 1990–99 2000–09	249	2.82 (1979–89) 7.96 (1990–99) 9.34 (2000–09)	Retrospective audit of hospital admission by discharge diagnosis (ICD-9-CM 446.9). Chart reviews were performed, and readmissions excluded. Case definition according to the AHA.[27]
Makino (2015)[15]	Asia	Japan	2011–12	26,691	243.1 (2011) 264.8 (2012)	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Lin (2015)[12]	Asia	Taiwan	1997–2010	13,179	49.1	Retrospective audit of hospitalisations by discharge diagnosis (ICD-9-CM 446.9). Cross referenced with IVIG use data.
Ha (2016)[35]	Asia	South Korea	2007–14	39,082	159.1–217.2	Retrospective audit of private health insurance claims data. No chart review. Annual estimates were used for graphs.

Continued...

Table 1.1 continued...

Study Name	Region	Country	Period	Cases	Incidence	Notes
Zhang (2016)[104]	Asia	Mongolia	2001–13	518	3.6	Retrospective audit of hospitalisations by discharge diagnosis (ICD-9-CM 446.9). Case reviews were performed. Case definition according to JKDRC.[105]
Singh (2016)[106]	Asia	India (Chandigarh)	2009–14	258	1.11–4.71	Single-centre retrospective case review. Case definition as per AHA.
Kim (2017)[107]	Asia	South Korea	2012–14	14,916	170.9–194.9	Retrospective surveillance through hospital surveys. Annual estimates were used for graphs.
Cimaz (2017)[18]	Europe	Italy	2008–13	2,901	14.7	Retrospective audit of hospitalisations by discharge diagnosis (ICD-9-CM 446.9). Case reviews not performed. Readmissions excluded.
Okubo (2017)[108]	North America	USA	2006 2009 2012	16,057	20.8 (2006) 19.1 (2009) 18.0 (2012)	Retrospective audit of hospitalisations by discharge diagnosis (ICD-9-CM 446.9). Case reviews not performed.
Sánchez-Manubens (2017)[109]	Europe	Spain (Catalonia)	2004–14	399	8.0	Prospective surveillance by case reporting.
Makino (2018)[110]	Asia	Japan	2013–14	13,675	302.5–308.0	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Manlhiot (2018)[39]	North America	Canada	2004–14	4,855	19.6	Passive surveillance and retrospective audit of hospitalisations by discharge diagnosis (ICD-10 M30.3).
Riancho-Zarrabeitia (2018)[42]	Europe	Spain	2004–14	3,737	11.7	Retrospective audit of hospitalisations by discharge diagnosis (ICD-9-CM 446.9). Case reviews not performed. Readmissions not excluded.
Tulloh (2019)[11]	Europe	UK & Ireland	2013–15	553	4.6	Prospective surveillance through case reporting to the BPSU.
Makino (2019)[111]	Asia	Japan	2015–16	31,595	309.0–330.2	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Chang (2019)[56]	North America	USA (Western New York)	2000–15	n/a	20.2	Retrospective chart review. Case definition according to the AHA.[27]
Xie (2020)[112]	Asia	China (Shanghai)	2013–17	2,447	94.7	Retrospective audit of hospital admissions by discharge diagnosis (ICD-9 446.9 or ICD-10 M30.3). Chart reviews not performed.

Continued...

Table 1.1 continued...

Study Name	Region	Country	Period	Cases	Incidence	Notes
Pasma (2020)[113]	Europe	Finland	1996–2016	711	6.7–17.9	Retrospective audit of hospital admissions by discharge diagnosis (ICD-10 M30.3). Chart reviews not performed.
Kim (2020)[16]	Asia	South Korea	2015–17	15,378	196.9	Retrospective surveillance through hospital surveys. Annual estimates were used for graphs.
Ae (2020)[40]	Asia	Japan	2018	17,364	359	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]
Mat Bah (2021)[21]	Asia	Malaysia (Johor)	2006–19	661	14.8	Prospective surveillance registry. Case definition according to the AHA.[28]
Robinson (2021)[114]	North America	Canada (Ontario)	1995–2017	4,346	22.0	Retrospective audit of hospital admissions by discharge diagnosis (ICD-9 446.9 or ICD-10 M30.3). Chart reviews not performed.
Taslakian (2021)[115]	North America	USA (Olmsted County, Minnesota)	1979–2016	124	21.4	Retrospective audit of hospital admissions by discharge diagnosis (ICD-9 446.9 or ICD-10 M30.3). Chart reviews were performed.
Gradoux (2022[22]**)**	Europe	Switzerland	2013–17	175	8.4	Prospective surveillance through case reporting to the SPSU.
Ae (2022)[7]	Asia	Japan	2019	17,347	371.0	Retrospective surveillance through hospital surveys. Case definition according to the JKDRC.[23]

Incidence is given as cases per 100,000 children under the age of 5 years per year. Traditionally, this means KD cases in children under the age of 5 years per 100,000 children under the age of 5 years per year, however that is not always specified and—in the case of Du (2007)—does not appear to be the case. AHA, American Heart Association; APSU, Australian Paediatric Surveillance Unit; BPSU, British Paediatric Surveillance Unit; HKKDSG, Hong Kong Kawasaki Disease Study Group; JKDRC, Japan Kawasaki Disease Research Committee; NZPSU, New Zealand Paediatric Surveillance Unit, SPSU, Swiss Paediatric Surveillance Unit.

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Chapter 2:
The Management of Kawasaki Disease

Part 1: Introduction

Early approaches to management of Kawasaki disease (KD) were guided by two seemingly apparent characteristics: that the condition was likely to have an infectious cause, and that it manifested as systemic inflammation. Thus, of Kawasaki's original cohort 94% received antibiotics and 40% received corticosteroids.[1] With the discovery of coronary arteritis identical to that seen in infantile periarteritis nodosa the role of corticosteroids was strengthened, albeit temporarily.[2,3] Additional clinical observations—namely thrombocytosis and fatal thrombosis, as well as arthritis—led to the use of aspirin, with two theorized roles: thromboprophylaxis and the suppression of inflammation.[4–8] Early trials of treatment protocols gave conflicting results, and none demonstrated a significant reduction in the incidence of coronary aneurysms.[3,9]

Intravenous immunoglobulin (IVIG) was the first treatment shown to significantly reduce the incidence of coronary aneurysms in KD, its early use having been informed by success in the treatment of idiopathic thrombocytopenic purpura.[10,10] The mechanism of action remains unclear,[10,11] however the effect size is undoubtable: with current protocols the incidence of aneurysms is reduced from over 25% to less than five percent.[12–14] Multiple meta-analyses have demonstrated the efficacy of IVIG in acute KD,[15–17] and it is now the cornerstone of KD management around the world.[18–21]

The aim of this review is to describe the current evidence for the management of acute KD and summarise major clinical practice guidelines. Except for the anti-platelet role of aspirin, agents used for thromboprophylaxis will not be reviewed here.

Clinical Practice Guidelines

Online sources were exhaustively reviewed for clinical practice guidelines on the management of acute KD; where an organisation had published multiple revisions of a guideline the most recent (as of December 2022) was used. The final list of documents is presented in **Table 2.1.1**.

Australia does not have a unified guideline on the management of KD, however that produced by the Royal Children's Hospital in Melbourne has recently been endorsed by the Paediatric Improvement Collaborative for use in Victoria, New South Wales, and Queensland—Australia's three most populous states.[22] Perth Children's Hospital also produces a guideline,[23] and a third is published by the non-for-profit publisher *Therapeutic Guidelines*.[24]

Table 2.1: Clinical Practice Guidelines for the Management of Acute Kawasaki Disease

Reference	Abbreviation	Region	Date
Webb, *et al.* Kawasaki Disease. Starship Children's Hospital[25]	NZ (2022)	New Zealand	2022
The Royal Children's Hospital. Clinical Practice Guideline on Kawasaki Disease.[22]	AU-RCH (2021)	Australia	2021
Perth Children's Hospital. Kawasaki disease.[23]	AU-PCH (2021)	Australia	2021
Gorelik, *et al.* 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease.[18]	ACR (2021)	North America	2021
Marchesi, *et al.* Revised recommendations of the Italian Society of Pediatrics about the general management of Kawasaki disease.[26]	ISP (2021)	Italy	2021
Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery, Committee for Development of Guidelines for Medical Treatment of Acute Kawasaki Disease. Guidelines for Medical Treatment of Acute Kawasaki Disease (2020 Revised Version).[27]	JSPCCS (2020)	Japan	2020
Shenoy, *et al.* Indian Academy of Pediatrics Position Paper on Kawasaki Disease.[28]	IAP (2020)	India	2020
Neudorf, *et al.* Guideline Kawasaki Syndrome. German Society for Pediatric Cardiology and Congenital Heart Defects.[29]	DGPK (2020)	Germany	2020
de Graeff, *et al.* European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease – the SHARE initiative.[20]	SHARE (2019)	Europe	2019
Barrios Tascón, *et al.* National consensus on diagnosis, treatment and cardiological follow-up of Kawasaki disease.[30]	AEP (2018)	Spain	2018
Nordenhäll, *et al.* National PM for Kawasaki's Disease.[31]	SW (2018)	Sweden	2018
Systemic Vasculitides – Kawasaki Disease. Therapeutic Guidelines.[24]	AU-TG (2017)	Australia	2017
McCrindle, *et al.* Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.[21]	AHA (2017)	North America	2017
Abate, *et al.* Enfermedad de Kawasaki: Consenso interdisciplinario e intersociedades.[32]	ASP/ASC (2016)	Argentina	2016
Holm, *et al.* Kawasaki disease. Danish Paediatric Society.[33]	DM (2015)	Denmark	2015
Brogan, *et al.* Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research.[34]	UK (2002)	United Kingdom	2002

Treatment Failure

Despite the success of IVIG, challenges remain. Persistence of systemic inflammation after treatment in a subset of patients—termed 'IVIG Resistance'—has been recognised since the first trials of IVIG for KD.[12] Children with IVIG resistance are at higher risk of developing coronary artery aneurysms.[35] Rates of resistance vary from less than 10%[36,37] to over 30%,[38] however the lack of a consensus definition for treatment failure makes comparisons challenging.[39] All definitions seek to identify the persistence of inflammation after the IVIG infusion, but with key differences around when and how this is determined. The American Heart Association (AHA) Scientific Statement on the Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease refers to IVIG resistance as "...recrudescent or persistent fever at least 36 hours after the end of the first IVIG infusion"[21]; by contrast Japanese guidelines refer to "...persistent fever after 48 hours of starting IVIG".[40] Other investigators have used a fall in the CRP as evidence of treatment response, with persistently elevated CRP incorporated into a definition of IVIG resistance[41] (of note, the AHA Statement explicitly warns against using the erythrocyte sedimentation rate for this purpose, as it is artificially increased after the administration of IVIG[21]). Finally, some authors use the term 'Refractory KD' to refer to ongoing inflammation after at least two doses of IVIG.[42,43]

With the recognition of increased risk of coronary aneurysm development in patients after treatment failure[35,44] there have been significant efforts to develop predictive tools for IVIG resistance (notably the Kobayashi,[45] Egami,[46] and Sano[47] scores). While these systems are used routinely in Japan,[48,49] poor test characteristics in other populations has limited their use.[50–53] The management of IVIG resistance is a topic of active research, with several treatment protocols under investigation.[41,54–57]

Part 2: Intravenous Immunoglobulin

Background

Intravenous immunoglobulin (IVIG) is a therapeutic product derived from the pooled plasma of human donors.[58] It contains polyclonal antibodies (mostly IgG[59]) and was initially used to treat disorders of humoral immunity such as agammaglobulinaemia.[58] Subsequent clinical experience with IVIG led to an appreciation of its immunomodulatory effects[60]—notably in the management of idiopathic thrombocytopaenic purpura (ITP),[61] which provided the rationale for early trials in KD.[10,10] IVIG is now approved for use in a wide range of clinical conditions,[62] and is considered the standard of care for KD.[21]

Mechanism of Action

Given the enigmatic nature of KD's aetiopathogenesis the mechanism of action of IVIG in the condition remains unclear.[63] Indeed, the anti-inflammatory actions of IVIG—central to its use in a diverse range of conditions—remain unclear.[60]

As mentioned, IVIG is composed almost entirely of the immunoglobulin class G (IgG). IgG is the predominant immunoglobulin class in humans and exemplifies the humoral component of the adaptive immune response.[64] IgG is a complex glycoprotein molecule (about 82–96% protein and 4–18% carbohydrate[64]) with two identical 'heavy chains' (bound to each other at the 'hinge' by a variable pattern of disulfide bonds), each bound to one of two identical 'light chains' (**Figure 2.2.1**). The IgG molecule is structurally and functionally divided into the Fab ('fragment antigen-binding') region, which acts to bind antigen in a highly-specific manner; and the Fc ('fragment crystalline') region, which mediates a range of regulatory and effector functions through interacting with a number of receptor molecules ('Fc receptors', FcR).[64,65] Four subclasses (IgG1, IgG2, IgG3, and IgG4) are defined by variations in the structure of the Fc region (and especially the hinge); their roles in human immunology is still poorly understood and as such they will not be discussed further in this review.[64–66]

In seeking to understand the mechanism of IVIG investigators have sought to distinguish effects attributable to the Fab region and Fc region. A number of actions have been attributed to the Fab region, including binding to and neutralising endogenous pro-inflammatory complement products C3b and C4b.[60,67–69] The predominant action of IVIG is, however, thought to be mediated by the Fc region.[67] In the original paper documenting the successful use of IVIG to treat ITP by Imbach *et al*,[61] the inhibition of platelet sequestration in the spleen by the saturation of Fc receptors on phagocytic cells of the reticuloendothelial system (now increasingly referred to as the

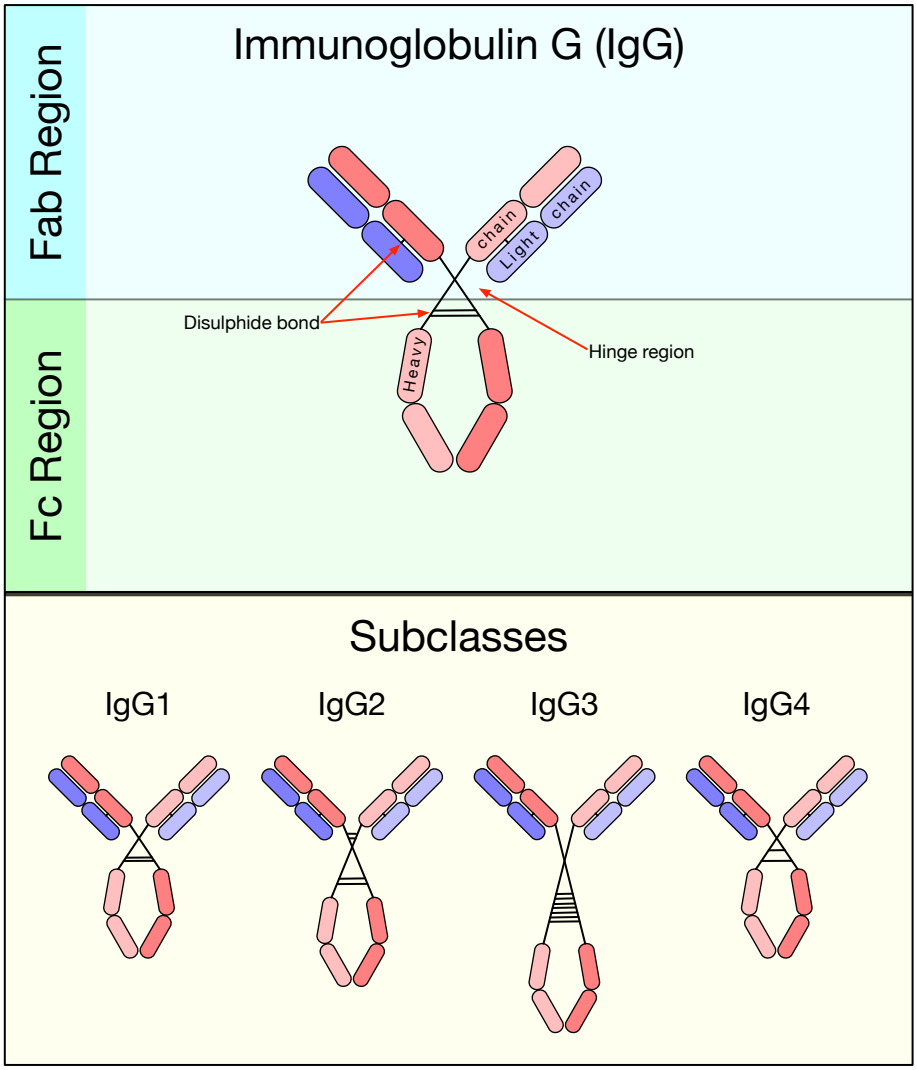

Figure 2.1: Structure of IgG and of different IgG subclasses.
a. IgG structure.
b. The different domains of Fab and Fc regions of IgG are indicated.

mononuclear phagocytic system,[70] MPS) was proposed. Three observations made this hypothesis likely: Firstly, while most cases of ITP are thought to be caused by destruction of platelet-directed autoantibodies, IVIG effectively raised the platelet count of patients with ITP and agammaglobulinaemia—arguing against the hypothesis that IVIG neutralised auto-antibodies (however Fc-dependent effects on auto-antibodies, such as by shortening auto-antibody half-life by competitive inhibition of the neonatal FcR, have been proposed[60]). Secondly, IVIG was ineffective at raising the platelet count of patients with ITP who had undergoing a splenectomy—indicating that the mechanism of action was at the point of sequestration. Finally, IVIG that had been treated with pepsin (which cleaves and inactivates the Fc region of the IgG molecule) was ineffective.[61] Debré *et al* would later demonstrate the efficacy of purified Fc fragments in ITP.[71] While current theories of the mechanism of IVIG in ITP have been refined, Fc-receptor saturation is still a central function.[70]

Other proposed Fc-dependent mechanisms of IVIG relate to the complex nature of IgG-FcR interactions *in vivo*, with different receptors capable of

directing pro-inflammatory and anti-inflammatory signal cascades on binding with the Fc ligand.[67,68] In KD proposed actions have included stimulating precursor T-cells to preferentially differentiate into regulatory T-cells (Tregs) in a manner mediated by interleukin 10 (IL-10) and possibly directed by dendritic cells.[63,72] While low circulating Treg numbers are seen in the acute phased of KD, a population of Fc-specific population has been observed in the peripheral blood of patients who have responded to IVIG (but not in those with IVIG resistance).[11,72] Other findings of interest (yet outside the scope of this review) include the inhibition of tumour necrosis factor (TNF)-α and matrix metalloproteinase 9 (MMP9) production in a mouse model of KD,[73] and significant evidence that polymorphisms in FcR genes can influence the disease course of KD.[74–78]

Manufacture and Supply

The manufacture of IVIG is resource-intensive and complex. Raw plasma (taken from both plasma donors and whole-blood donors) is pooled,[79] with each pool containing plasma from between 1,000 and 100,000 individual donors.[80] Donated blood is screened for infectious hazards (including viruses, bacteria, and prions) and undergoes multiple viral inactivation procedures to minimise the risk of transfusion transmitted infections.[80] This is followed by fractionation to separate immunoglobulins from other plasma proteins; most modern processes are based on the cold ethanol fractionation described by Cohn in 1946,[81] however some (including *Intragam*®10, commonly used for the treatment of KD in Australia) use the newer chromatographic fractionation process.[80,82]

Early attempts at intravenous infusion of human immunoglobulin were complicated by high rates of adverse reactions; these were attributed to direct complement activation, which was thought to be dependent on the Fc region of the IgG molecule.[83,84] In response, manufacturers introduced pepsin fragmentation, wherein the Fc region of the IgG molecule was proteolytically removed.[84] Subsequent processes included the use of plasmin (which cleaves the IgG molecule at fewer locations than pepsin, resulting in fewer fragments[83]) and chemical modification of the Fc region (including sulphonation, alkylation, and β-propiolactonation) to reduce complement activation.[83,85] All of these methods resulted in reduced half-life and efficacy (especially opsonisation).[83,84] Modern manufacture methods seek to preserve the integrity of the IgG molecule and the *in vitro* function of the Fc region.[85]

Immunoglobulin composition is carefully controlled: ABO blood group antibody titres are reduced due to the risk of haemolytic reactions[85] and IgA is removed due to the risk of anaphylaxis in those with IgA deficiency.[86,87] Modern IVIG formulations are almost entirely whole IgG (over 98% in the

case of *Intragam*[*]) as monomers and dimers, with IgG subclass ratios ideally matching that of normal human plasma.[59]

IVIG is manufactured in Australia by CSL-Behring at its facility in Melbourne, with IVIG derived from Australian donors offered under the brand *Intragam*[*].[59] The Commonwealth Government of Australia funds the provision of IVIG for the treatment of selected conditions under the National Blood Agreement with the various States and Territories.[88] Strict criteria govern the use of publicly-funded IVIG,[62] with KD an approved indication since the first guidelines were published in 1993.[89] Australian Red Cross Lifeblood (formerly the Australian Red Cross Blood Service) is responsible for the distribution of publicly-funded IVIG.[90] Five brands are available in Australia (*Intragam*[*], *Privigen*[*], *Flebogamma*[*], *Gamunex*[*], and *Octagam*[*]),[90] however *Intragam*[*]10 (10% IgG by weight) is preferentially approved for the treatment of KD.[91]

Resource Stewardship and Pharmacoeconomics

Human immunoglobulin is an expensive resource.[92] Pharmacological products have high initial costs, including those associated with research and development, capital costs of manufacturing facilities, regulatory compliance, and patent acquisition.[93–95] The marginal cost of production[*] falls as economies of scale are realised; this, along with market pressures enabled by patent expiry, lead to price reductions in the long term. The economics of blood products is different: the high ongoing cost of collecting, testing, and processing blood from human donors results in a marginal cost of production that is both fixed and high, such that market price largely reflects marginal costs.[96] Furthermore, globalised and logistically complex supply chains are vulnerable to disruption (as was seen during the COVID-19 pandemic[97–99]) leading to supply-demand imbalances and price fluctuations.[100,101] Demand for all immunoglobulin products has been increasing both internationally and locally.[102–104] Domestic production, which previously accounted for over 90% of immunoglobulin supplied in Australia, now only accounts of 57%.[103] IVIG is used at a relatively high dose in the management of KD (2 g/kg), yet the small absolute quantity required for infants and young children means that KD represents a trivial burden on national supply: of the 4.98 million grams of immunoglobulin supplied in Australia in 2015-16 only 15,046 grams (0.3%) was for KD).[103] By contrast in Japan—where the incidence of KD is more than an order of magnitude higher than in Australia[105,106]—KD ranks third for IVIG consumption, after IgG2 deficiency and chronic inflammatory demyelinating polyneuropathy[102]).

[*] The marginal cost of production is the additional cost incurred to produce additional product. Economy of scale is largely achieved through diminishing marginal costs.

Few studies have assessed the cost effectiveness of IVIG for acute KD. A 1993 Canadian study modelled the costs incurred in the first seven weeks after diagnosis for 100 children with KD treated with either IVIG or aspirin, concluding that the use of high-dose IVIG (preventing an estimated 14 cases of coronary dilatation) resulted in savings of C$323,400 (in 1992 Canadian dollars, equivalent to AUD$653,142 in 2022).[107] Healthcare costs—including the cost of IVIG—vary markedly around the world,[108,109] making direct comparisons challenging. Health systems also differ in the cost burden that is borne by patients: in Australia IVIG is provided for approved conditions at no extra cost to the patient[103,108]; in other countries families may need to purchase IVIG for their child's treatment at prohibitive cost.[110] A number of strategies have emerged in response to the resource constraints of IVIG: patient selection based on predicted disease severity,[49] dose selection based on predicted disease severity,[48,111] and the use of agents other than IVIG.[110,112]

Primary Therapy for Acute Kawasaki Disease

The use of IVIG for the management of KD was first described by Furusho *et al* in 1983 in a semi-randomised, non-blinded trial with (predominantly) historical controls.[10,113] Fourteen patients with KD received IVIG 400 mg/kg daily for five days (replicating the protocol for ITP described by Imbach *et al*[61]), controls received aspirin 10–30 mg/kg/day for at least 3 months. Those given IVIG had a shorter time to defervescence and normalisation of C-reactive protein (CRP), and had no coronary aneurysms seen on coronary angiography (compared with aneurysms in 17% of the control patients). These findings were corroborated in a small multi-centre unblinded randomized controlled trial by the same investigators one year later[10] and confirmed in an independent American investigator-blinded randomised controlled trial two years after that.[114] The latter study was stopped prematurely due to the significant evidence of benefit from IVIG.[63]

A Cochrane Review in 2003 identified 11 studies that compared IVIG to placebo for the management of acute KD,[114–119] of which seven were included in a meta-analysis.[15] There were significantly fewer new coronary abnormalities at thirty days among those treated with IVIG versus placebo (relative risk 0.74, 95% confidence interval 0.61 to 0.90); heterogeneity between studies due to different IVIG doses was addressed in subgroup analyses, with a significant reduction in aneurysms observed for doses of 500 mg/kg, 1,200 mg/kg, and 1,600 mg/kg. Among children with no coronary abnormalities at enrolment, those who received IVIG had significantly fewer coronary artery abnormalities at 30 days but not at 60 or 180 days; among those with coronary abnormalities at enrolment there were no significant differences between treatment and control groups at any timepoint.[15] In light of more recent studies, and refinements in the methodological approach to meta-analyses, Broderick *et al* have published a protocol for an updated

systematic review and meta-analysis of IVIG for KD for the Cochrane Collaboration.[120] Evidence permitting, it will be important to quantify the treatment effect at various timepoints—especially beyond six months post-treatment.

Immunoglobulin Dose

When appropriately powered, trials of IVIG for acute KD have consistently reported a positive correlation between dose and efficacy,[12,115,121] with single large dose regimens outperforming multiple small dose regimens.[12] This lead to the hypothesis that peak serum IgG concentration was of critical importance in terminating the inflammatory process of KD.[122] Recent studies have provided further evidence for this hypothesis, with higher post-infusion serum IgG concentrations associated with lower rates of treatment failure and coronary artery aneurysms.[123] The optimal dose of IVIG to prevent coronary aneurysms has been assessed in several studies and systematic reviews and meta-analyses,[15,17,124] out of which has emerged a general consensus in favour of a single dose of 2 g/kg—both in clinical practice guidelines[21,27,125] (**Table 2.2.1**) and clinical practice.[126]

Challenges to this consensus have repeatedly been mounted, especially in Japan where the high incidence of KD has significant implications for national IVIG supply.[48,49,127] Shiraishi *et al*[49] described a study protocol in which children were initially treated with IVIG 1 g/kg with those who failed primary therapy going on to receive additional higher doses.[49] The study did not recruit a control arm but compared the rate of coronary aneurysms in there cohort with that previously reported from nation-wide surveys, reporting lower rates of aneurysms in their cohort. Matsuura *et al*[48] reported the outcomes from a study in which treatment was stratified based on the patient's Kobayashi score.[45] Those at highest risk received IVIG 2 g/kg plus primary adjunctive corticosteroid, those at moderate risk received IVIG 2 g/kg, and those at low risk received IVIG 1 g/kg. There were no significant differences between groups either in time to defervescence or the risk of coronary artery aneurysms. While poor performance of scoring systems outside of Japan makes direct comparison difficult,[128] these studies suggest the possibility of a stepwise approach to IVIG dosing in KD.

Finally, Suzuki *et al*[111] retrospectively reviewed treatment records to compare the efficacy of low-dose IVIG (1 g/kg) versus high-dose IVIG (2 g/kg) for children over 25 kg bodyweight. They found no significant differences between low-dose and high-dose IVIG in terms of length of stay, rate of treatment failure, or rates of coronary artery aneurysms, noting that the cost of treatment was significantly higher for those in the high-dose group. Although limited by the retrospective study design, these results suggest that

it may be time to reconsider the current weight-based approach to dosing of IVIG in KD.

Infusion Duration

Despite evidence favouring single large doses of IVIG there remains a lack of consensus around the duration of the infusion (**Table 2.2.1**). Shorter infusion times (dose given over 10–12 hours) are typical in North America,[21] while longer infusion times (12–24 hours) are preferred in Japan[106]; European guidelines vary between these, with some ending even shorter infusions.[125] The National Blood Authority of Australia recommends that the infusion be given over 10–12 hours.[129]

When to Treat

Trials of IVIG for acute KD defined inclusion and exclusion criteria in an attempt to reduce heterogeneity within the cohorts; children who were unable to be treated within a defined period of time from the onset of fever were often excluded. Furusho *et al* excluded children who could not be treated within 7 days of fever onset,[10] while Newburger *et al* excluded those with a duration of fever greater than 10 days.[12,114]These late cut-offs for commencing IVIG started to appear in expert recommendations,[130] and for a time there was a perception that treatment after day 10 was not indicated.[131] Early guidelines responded by emphasising that IVIG should be given within 10 days wherever possible, but that delayed diagnosis ought not necessarily preclude treatment.[132] Statements to this effect are included in published guidelines to this day (**Table 2.2.1**).

The problem of how to manage children presenting late in the course of KD is an important one—indeed up to 20% of patients may fall into this category.[133] A small number of studies have investigated the efficacy of IVIG in patients with delayed diagnosis of KD. Sittiwangkul *et al* retrospectively reviewed the cases of 170 children with KD at one institution in Thailand, of whom 20 were diagnosed after day 10 of fever.[134] They observed higher rates of coronary artery aneurysms among those treated after day 10 of fever, however due to small case numbers were not able to assess the significance of this at 1 year follow-up. While those treated after day 10 of fever had higher rates of treatment failure, 70% (12/17) still defervesced after a single dose of IVIG. Muta *et al* compared response to treatment and coronary outcomes in 150 Japanese patients who received IVIG between day 11 and day 20 with age- and gender-matched historical controls.[135] They found no difference in rates of defervescence after IVIG but much higher rates of coronary artery aneurysms among those treated after day 10 of fever. Considering only those patients without coronary aneurysms at the time of treatment rates of aneurysm development were identical during the acute phase (up to one month after treatment), with no statistically significant difference between groups in the convalescent phase (more than one month after treatment).[135] Unfortunately,

by treating time-to-treatment as a categorical variable (≥10 days *versus* >10 days) the possible benefits of IVIG on day 11 (for example) are obscured. Qui *et al*, in a retrospective analysis of 930 Chinese KD patients, treated time-to-treatment as an ordinal variable in logistic regression analysis with coronary aneurysms (at three timepoints) as the outcome variable.[136] They found that time-to-treatment was positively associated with the risk of coronary artery aneurysm at 1 month (odds ratio [OR] 1.17, 95% confidence interval [CI] 1.10 to 1.25, P <0.001) and 6 months (OR 1.17, 95% CI 1.06 to 1.28, P = 0.002), but not at 12 months (OR 1.11, 95% CI 0.94 to 1.31, P = 0.226). Unfortunately, the marginal effect of time-to-treatment at each day was not presented, so the efficacy of IVIG beyond ten days was difficult to appreciate.

This issue was finally addressed in a large retrospective analysis of coronary outcomes in a Dutch KD cohort by van Stijn *et al*.[137] They estimated the cumulative distribution of time-to-treatment per day in patients with no coronary involvement, as well as small, medium, and giant aneurysms. Time-to-treatment was correlated with the development of medium (OR 1.1, 95% CI 1.1 to 1.2, P <0.001) and giant aneurysms (OR 1.2, 95% CI 1.1 to 1.2, P <0.001), but not small aneurysms (OR 1.0, 95% CI 1.0 to 1.1, P = 0.6). Importantly, there was no specific cut-off point at which treatment was deemed ineffective. While this study sought to address an important question regarding the efficacy of late IVIG it had two significant limitations. Firstly, the authors acknowledge the risk of selection bias, as most patients were referred to their institution after having received initial therapy at a smaller hospital and were therefore likely to represent the more severe end of the disease spectrum. Indeed, the rates of aneurysm formation in the cohort were extremely high (22.8% of those who received IVIG developed coronary aneurysms). Secondly, while we are told that coronary outcomes were assessed within 8 weeks of fever onset the exact timing is not given. The efficacy of IVIG among those with or without aneurysms at the time of treatment, and whether a difference is seen at long-term follow-up, remains unclear.

Several investigators have observed equal or lower rates of retreatment among those treated after day 10 of fever versus those treated earlier.[138–140] While this has been interpreted as evidence that the anti-inflammatory effect of IVIG persists after 10 days, it may simply reflect the natural history of the condition—most of Kawasaki's original cohort defervesced spontaneously between day 9 and day 11 despite the lack of an effective treatment.[1]

The efficacy of IVIG early in the course of acute KD has also been studied. Tse *et al* found that treatment on or before day 5 of fever was associated with better coronary outcomes at 1 year,[141] however other studies have given conflicting results. Muta *et al*, comparing treatment on or before day 4 with treatment after day 4, observed similar coronary outcomes between groups.[142] In a

systematic review and meta-analysis of early IVIG for acute KD Yan *et al* reported a lack of evidence for an improvement in coronary outcomes with early IVIG as the upper bound of the 95% confidence interval for the odds ratio was 1.00.[143] They noted significant heterogeneity between studies however, and on subgroup analysis the studies from China and America did show a statistically significant benefit for early IVIG whereas studies from Japan did not. As was the case for studies of late IVIG however, treating time-to-treatment is likely to obscure important effects, especially as KD is known to be diagnosed and treated earlier in Japan than elsewhere (and so the relative distributions within each group are likely to be different in Japan as compared with other countries).[144]

The evidence that early treatment is associated with higher rates of retreatment is stronger.[38,145,146] In their meta-analysis Yan *et al* reported that early treatment was significantly associated with retreatment (OR 2.24, 95% CI 1.76 to 2.84, P <0.001), but again noted significant heterogeneity—due, in part, to different definitions for treatment failure resulting in widely varying rates of retreatment between studies.[143]

Preparation Variables

IVIG preparations vary widely in production methods, IgG concentration, stabilization additives, as well as the concentration of other immunoglobulin classes (such as IgA).[80,85,147] Harada observed reduced efficacy with pepsin-treated immunoglobulin than with intact immunoglobulin[115]; this suggests that the Fc region of the IgG molecule may play a crucial role in the treatment of KD.[60,63] Tsai *et al* compared the efficacy of four brands of IVIG available in Taiwan, observing significantly lower efficacy in one brand (*Intraglobulin*F*) in terms of treatment failure and coronary aneurysm formation.[148] Unlike the other brands studied *Intraglobulin*F* was manufactured using β-propiolactonation, which was hypothesised to significantly modify the Fc region.[85,148] Lin *et al* observed higher rates of treatment failure, but not coronary artery aneurysm formation, in patients who received *Intraglobulin*F*.[149]

As IVIG manufacturing processors have moved away from methods that significantly modify the Fc region other variables have been shown to affect efficacy. Manlhiot *et al* compared outcomes among children with KD treated with two immunoglobulin brands available in Canada; *Gamimune** was associated with lower rates of retreatment but higher rates of coronary artery aneurysms when compared with *Iveegam**.[147] While neither product was manufactured using a process known to affect the Fc region, *Gamimune** had significantly higher titres of IgA. Additionally, each used a different stabilisation process: glucose in the case of *Iveegam** and acidification in the case of *Gamimune**. Lin *et al* also reported higher rates of coronary aneurysms

among children who received acid stabilised IVIG products (including *Gamimune*®).[149] The authors of both papers hypothesised that the acidifying action of *Gamimune*® might contribute to elastin degradation and exacerbate aneurysm formation.

Finally, the effect of IVIG concentration on efficacy has been considered by several investigators. In the study already mentioned Manlhiot *et al* observed that *Gamimune*® (10% concentration) had lower rates of treatment failure than *Iveegam*® (5% concentration), hypothesising that the additional time required to infuse *Iveegam*® resulted in greater duration of fever (importantly, treatment failure in that study was defined as persistence of fever 36 hours after the *start* of the IVIG infusion).[147] Other investigators have reported contrasting results: both Han *et al* and Downie *et al* observed higher rates of treatment failure with 10% IVIG preparation than with 5% preparations,[150,151] although with both using different definitions of treatment failure.

While *Intragam*®10 (which is preferentially administered for KD in Australia) does not undergo any processes known to affect the Fc region, it is acid stabilised and presented at 10% concentration.[59] The suggestion that these product variables may affect efficacy in KD is of interest, however a lack of consensus around key definitions prevents useful synthesis of the evidence at this time.

Secondary Therapy After Treatment Failure

Retreatment using additional doses of IVIG was one of the first-reported therapies for IVIG resistance, proving to be both safe and effective.[44,152] Current guidelines recommend additional doses of IVIG after treatment failure, but acknowledge a lack of evidence from large controlled trials.[20,21,27]

Adverse Reactions and Interactions

The reported incidence of adverse reactions varies substantially, with most authors describing rates of between 30% and 40%.[87,153] The significant majority of adverse reactions are mild and self-resolving, however life-threatening reactions (including haemolysis and thromboembolism) have been reported.[154,155] IVIG can also interfere with seroconversion in response to live vaccines, an issue of particular relevance to children treated for KD.[156]

Mild Immediate and Delayed Infusion Reactions

Immediate infusion reactions related to KD (such as headache, chills-fever, fatigue, dyspnoea, nausea, and hypotension) are common and typically mild.[87,153] While the cause of these reactions is not clear complement activation and IgG aggregates have been implicated.[84,87] Immediate reactions usually occur within the first 30 minutes of the infusion and often respond to a reduction in the infusion rate—indeed, current infusion protocols often utilise a stepped infusion rate for this reason.[87,157,158] Premedication with

antihistamines, antipyretics, and anti-inflammatory drugs (both non-steroidal and steroidal) have been advocated,[87] however there is conflicting evidence around efficacy.[159,160] Liu *et al*, in a single-centre retrospective audit of premedication practices for patients treated for KD, observed high rates of premedication use but significant variability in agents used.[161] Currently evidence is lacking to guide premedication choice in KD.

Delayed infusion reactions occur after the infusion has ended, and are very common, with headache, fatigue, and abdominal pain being most frequently reported. Headache can last for over a day and can significant limit function.[153] Headaches occasionally display features consistent with migraine (including visual changes), and aseptic meningitis can rarely occur. While most guidelines recommend reducing the infusion rate, this is clearly not relevant in cases of delayed reactions.[153] There is a need for further research to guide the prevention and management of delayed infusion reactions.

Haemolysis

Acute haemolysis due to IVIG—while rare—is well recognised,[162] with those receiving IVIG for KD at particularly high risk.[163–165] The cause is theorised to be passive transfer of anti-A and anti-B IgG to recipients carrying incompatible ABO antigens,[166] although conflicting evidence suggests that other mechanisms may be involved.[167] Modern IVIG preparations are designed to meet regulated maximum titres of anti-A and anti-B (commonly no higher than 1:64) but actual titres vary between products.[166] Bruggeman *et al* observed a significant increase in the rate of haemolysis among children receiving IVIG for KD in Canada following the introduction of IVIG preparations with relatively high anti-A and anti-B titres.[166] Given the relatively high risk of this phenomenon when using IVIG to treat KD clinicians must remain vigilant to changes both at the level of the individual patient and the population receiving IVIG more generally.

Thrombosis

The infusion of high-dose IVIG has been associated with intravascular thrombosis.[168–170] While most cases have been reported in adults, strokes have occurred in children receiving IVIG for KD.[155] The mechanism of IVIG-associated thrombosis remains unclear, with conflicting evidence of an effect on blood viscosity.[171–173] Despite the rarity of the phenomenon it is of particular relevance in the case of KD, for two reasons. Firstly, marked thrombocytosis and platelet activation mean that KD is a pro-thrombotic state.[171,174,175] Secondly, vascular changes (including both aneurysm and arterial spasm) can result in altered tissue perfusion.[176,177] Indeed, cerebral hypoperfusion has been observed in acute KD,[178] and cerebral infarctions have occurred independent of IVIG administration.[179,180] While there has been little research to quantify the risk of IVIG-associated thrombosis in KD, clinical

deterioration consistent with thromboembolic disease should prompt immediate consideration of this phenomenon.

IVIG and Live Vaccines

Passively acquired polyclonal antibodies (such as from IVIG) can interfere with seroconversion following immunisation with live attenuated vaccines.[156] Measles-containing vaccines are live-attenuated vaccines that are typically administered in the first few years of life—the peak age of incidence of KD. National immunisation guidelines recommend postponing the administration of live vaccines after IVIG for the treatment of KD, however there is no international consensus regarding the period of postponement;[181] North American, and Australian and New Zealand guidelines recommend postponing live vaccines for 11 months after IVIG[21,182–186]; European[20] and Japanese[40] guidelines recommend a 6 month postponement. Further work is needed to understand the duration of this effect to better inform immunisation guidelines.

Clinical Practice Guidelines

There is unanimous consensus around the use of IVIG at a dose of 2 g/kg in a single infusion for acute KD (**Table 2.2.1**). Where multiple small-dose protocols were discussed it was always for exceptional circumstances (namely congestive cardiac failure wherein the volume of a single high-dose infusion was problematic).[31,34] Recommended infusion times varied, however most guidelines recommend that the full dose be given within 12 hours. No guideline advised against administering IVIG too early in the disease course, and all allowed for the administration of IVIG after day 10 if there was evidence of ongoing inflammation (or made no reference to this). Only one guideline discussed pre-medication.[32]

Table 2.2: Clinical Practice Guidelines for the Use of Intravenous Immunoglobulin as Primary Therapy in Acute Kawasaki Disease

Guideline	IVIG Dose	Infusion Duration	When to Treat	Comment
NZ (2022)[25]	2 g/kg single dose	Over 10–12 hours (but notes that infusion rates differ between the two available products: *Privigen*® and *Intragam*®*P*)	"...should be given when the diagnosis is strongly suspected" and within 10 days of fever, but: "IVIG should still be administered later than 10 days if there are signs of continuing inflammation (fever, high ESR) or evolving coronary artery disease."	
AU-RCH (2021)[22]	2 g/kg single dose	Not given (provided in other institutional documents).	"...on diagnosis" and within 10 days of fever, but: "...should also be given to patients diagnosed after 10 days of illness if there is evidence of ongoing inflammation."	
AU-PCH (2021)[23]	2 g/kg single dose	Over 8–12 hours	Not given	
ACR (2021)[18]	2 g/kg single dose	Not given	Not given	
ISP (2021)[26]	2 g/kg single dose	Over 12 hours (16–24 hours if signs of cardiac failure)	Within 10 days (ideally 7), but: "Treatment before the 5th day of fever should be reserved to exceptional cases of unequivocal diagnosis of KD" And: "IVIG should also be administered to children presenting after the 10th day of illness in case of persistent fever or ongoing systemic inflammation."	
JSPCCS (2020)[27]	2 g/kg single dose, or 200–400 mg/kg/day for 3–5 days (although this is acknowledged as less effective and said to be for exceptional circumstances)	Over 12–24 hours	No clear recommendations; preference for treatment within 7–9 days.	
IAP (2020)[28]	2 g/kg single dose	Over 12–24 hours	Within 10 days (ideally 7), but: "IVIG should be considered even in patients with >10 days of illness with persistent fever, systemic inflammation evidenced by elevated ESR or CRP (>3.0 mg/L), or presence of CAAs."	

Continued...

Table 2.2 continued...

Guideline	IVIG Dose	Infusion Duration	When to Treat	Comment
DGPK (2020)[29]	2 g/kg single dose	Over 10–12 hours	"If the diagnosis is made early, before the 5th day of illness, the administration of IVIG should not be delayed." And: "Even if the diagnosis is made later (>10 days), IVIG application still makes sense if there are signs of inflammation, fever, and coronary abnormalities."	
SHARE (2019)[20]	2 g/kg single dose	Not given	"As soon as a patient is diagnosed with KD, treatment should be initiated."	
AEP (2018)[30]	2 g/kg single dose	Over 12 hours	"...as soon as possible in the first 10 days of illness or even later if febrile symptoms of unknown origin persist, persistent inflammatory activity confirmed by increased CRP or ESR, or the presence of coronary aneurysms."	This document recommends that 5% IVIG be used for the first administration in an individual, and that all infusions should be commenced at a lower rate for the first 30 minutes.
SW (2018)[31]	2 g/kg single dose (but can be split over 2 days if signs of heart failure)	Over 8–12 hours	"Treatment is started as soon as the diagnosis is made, preferably within 7 days of the onset of symptoms, but should also be given if the diagnosis is made later."	
AU-TG (2017)[24]	2 g/kg single dose	Over 10–12 hours	Not given	
AHA (2017)[21]	2 g/kg single dose	Over 10–12 hours	"As early as possible..." and within 10 days of fever, but: "IVIG should also be administered to children presenting after the tenth day of illness if they have ongoing systemic inflammation as manifested by elevation of ESR or CRP (CRP >3.0 mg/dL) together with either persistent fever without other explanation or coronary artery aneurysms (luminal dimension Z score >2.5)."	

Continued...

Table 2.2 continued...

Guideline	IVIG Dose	Infusion Duration	When to Treat	Comment
ASP/ASC (2016)[32]	2 g/kg single dose	Over 10–12 hours	"...between days 5 and 10 of the onset of the disease", but "If the diagnosis is made after 10 days of illness, treatment with g-GEV in patients with fever and persistently elevated acute phase reactants or in the presence of coronary aneurysms."	This document also recommends the use of diphenhydramine 1 mg/kg as premedication 1 hour before the infusion.
DM (2015)[33]	2 g/kg single dose	Over 6–8 hours	Not given	
UK (2002)[34]	2 g/kg single dose (but can be split over 2–4 days in infants with cardiac failure)	Over 12 hours	"IVIG treatment should be started early in the disease, preferably within the first 10 days of the illness. Importantly, however, clinicians should not hesitate to give IVIG to patients who present after 10 days if there are signs of persisting inflammation."	

Conclusions

IVIG is well established as a treatment for KD, with high-level evidence that it reduces the rate of coronary artery development. While clinical practice guidelines unanimously endorse a dose of 2 g/kg there is emerging evidence to suggest that a more nuanced approach to dosing (either stratifying by disease severity or bodyweight) may be safe. Issues around the global supply and logistics of IVIG may mean that innovation in this area is needed.

There is some evidence that a range of administration and product variables might lead to variable response to treatment, yet the lack of a consensus definition of treatment failure makes this difficult to discern. There is a need for global collaboration around an agreed definition of treatment failure to strengthen research in this important area.

Part 3: Aspirin

Background

Aspirin (acetylsalicylic acid) has been used in the management of KD since at least the 1970s,[5–7] with early recognition of theoretical benefits both from aspirin's antiplatelet effects and anti-inflammatory effects.[4,5] The appropriate dose of aspirin during the acute phase of the disease has been a point of controversy almost since the first reports of its use, with current guidelines and practice varying substantially.[20–22,27] Most guidelines recommend that children receive moderate-dose aspirin (30–50 mg/kg/day in divided doses) until defervescence, at which point low-dose aspirin (3–5 mg/kg/day in a single dose) is commenced.[20,25,27,28,187] American guidelines allow for aspirin to be started in the high-dose (80–100 mg/kg/day in divided doses) or moderate-dose range before reducing to the low-dose range.[21] Australian recommendations differ: Therapeutic Guidelines discusses high-dose and moderate-dose aspirin in the acute phase without providing a recommendation, and recommends that low-dose aspirin be commenced after defervescence.[24] In contrast, guidelines published by the Royal Children's Hospital in Melbourne (which have been endorsed by the Paediatric Improvement Collaborative for use in Victoria, New South Wales, and Queensland) and the Perth Children's Hospital only recommend the use of low-dose aspirin[22,23]; the Australian Medicines Handbook Children's Dosing Companion similarly recommends low-dose aspirin.[188] This recommendation is unusual at a national level—only Swedish guidelines gave similar advice.[31,125]

History of Aspirin Dosing in Kawasaki Disease

Before the effective treatment of KD with IVIG investigators theorised that aspirin might be a useful agent with two important actions: amelioration of the inflammatory process by inhibiting COX-2-dependent synthesis of prostaglandin E_2 (a pro-inflammatory eicosanoid) and prevention of thrombosis by inhibiting COX-1-dependent synthesis of thromboxane A_2 (responsible for platelet activation).[4,8,189–191] There was even hope that aspirin might prevent the development of coronary artery aneurysms.[192]

While COX-1 inhibition occurs selectively at very low plasma salicylate concentrations, COX-2 remains active until relatively high concentrations are reached.[190] Early investigators struggled to achieve plasma salicylate concentrations needed for COX-2 inhibition (theorised to be 200 mg/L[6])—variably attributed to impaired intestinal absorption[6] or enhanced renal clearance[193] and thought to be unique to KD[194]—leading to the use of extremely high doses of aspirin (up to 200 mg/kg/day[6]). Around the same time other investigators were raising concerns of a possible paradoxical pro-thrombotic effect of aspirin at high doses through inhibition of COX-2-dependent synthesis of prostacyclin by vascular endothelial cells.[8,195,196]

(Indeed, recent studies have confirmed that platelet activation can occur in the presence of high plasma salicylate concentrations through non-COX-dependent mechanisms.[197]) This was felt to be particularly concerning due to the erratic and unpredictable patterns of intestinal salicylate absorption in the acute phase of the disease.[8] These findings resulted in divergent recommendations for aspirin dose in acute KD by the mid-1980s.[4,8,192]

Aspirin as Primary Therapy for Acute Kawasaki Disease

The first intervention trial for acute KD compared five treatment protocols, of which two included aspirin (30 mg/kg/day) during the acute phase:[3]

Protocol 1:	Prednisolone + Cephalexin (n = 17)
Protocol 2:	Prednisolone + Warfarin + Cephalexin (n = 7)
Protocol 3:	Prednisolone + Aspirin + Cephalexin (n = 7)
Protocol 4:	Aspirin + Cephalexin (n = 36)
Protocol 5:	Cephalexin alone (n = 25)

In all cases cephalexin was discontinued when the possibility of a bacterial infection had been excluded. The investigators observed vastly differing rates of coronary aneurysms between the groups—highest among those who received protocols 1 and 2 and lowest among those who received protocols 3 and 4; there was no significant difference in the rates of aneurysms between those who received protocols 4 and 5. This study had two very significant impacts on the management of acute KD: corticosteroids were (for a time) contraindicated,[9,198] and the importance of aspirin was elevated—even as investigators acknowledged the equivalent outcomes for aspirin versus cephalexin alone.[192,199] Only one other study compared coronary outcomes by aspirin dose prior to the introduction of IVIG; Ichida *et al* described a cohort of 110 children with KD in New York, finding no difference in the rates of aneurysm formation by aspirin dose.[200]

With the recognition of IVIG as an effective treatment for KD many investigators included aspirin dose as a study variable in IVIG trials. Durongpisitkul *et al* undertook what would be the first of many meta-analyses of these trials.[16] They found no evidence that high-dose versus low-dose aspirin (in combination with high-dose IVIG) resulted in fewer coronary aneurysms at 30 or 60 days post-treatment, however none of the included trials used randomised treatment allocation for aspirin dose. Baumer *et al* undertook a systematic review for the Cochrane Collaboration in 2006, but concluded that the available evidence was of insufficient quality to inform any recommendations.[201]

More recent studies of aspirin dose have often used time to defervescence or rate of treatment failure (the latter usually defined by the former) as surrogate end points for assessing efficacy.[202] While low-dose aspirin has occasionally

been associated with longer duration of fever[202] and higher rates of treatment failure[203] other studies have observed no significant differences.[204–207] None of these studies reported differences in rate of coronary aneurysms.

Three further meta-analyses have assessed the impact of aspirin dose on outcomes. Zheng *et al* reviewed six studies for coronary outcomes, five studies for treatment response, and four studies for duration of fever and hospitalisation—they found no evidence that aspirin dose meaningfully influenced any of these outcomes.[208] Jia *et al* did find a small reduction in the duration of fever with high-dose aspirin, although the effect was entirely dependent on one study.[209] Moreover, aspirin dose had no effect on rates of aneurysm formation or response to treatment.[209] Finally Chiang *et al* pooled data for patients who received low-dose aspirin and no aspirin; rates of coronary artery lesions were lower in the low-dose/no aspirin group than in the high-dose aspirin group (odds ratio 0.81, 95% confidence interval 0.69 to 0.95, $p = 0.01$). There was no statistically significant association between aspirin dose and treatment response.[210]

Aspirin for Thromboprophylaxis in Kawasaki Disease

Thromboprophylaxis is recommended in the acute phase of KD (and significantly longer in those with coronary aneurysms) given the risk of thrombosis and consequent myocardial infarction.[21] Children with KD are at risk for arterial thrombosis due to a number of predisposing factors, with the risk of thrombosis influenced by the extent of coronary (and systemic) artery disruption, timepoint in the disease process, pharmacotherapy, and a range of other variables.

Risk of Thrombosis in Kawasaki Disease

Arterial thrombosis (particularly of the coronary arteries) is the leading cause of death in KD; the risk of death being highest in the acute phase (within two months of presentation).[211] Thrombosis typically complicates aneurysms (both of the coronary[212–214] and systemic[215,216] arteries), but have been observed to occur in KD without demonstrable arterial disruption.[217] With widespread use of IVIG the incidence of coronary aneurysms has reduced remarkably, however they still occur in 2–9% of cases.[37,106,218–220] The development of aneurysms starts early in the disease, with dilatation visible on transthoracic echocardiogram as early as day 4.[221] Dilated vessels can follow different trajectories: spontaneous resolution occurs in approximately 80%.[222,223] Small- and medium-sized aneurysms are capable of spontaneous regression,[222,224–226] however the mechanisms by which this occurs (including luminal myofibroblastic proliferation, intimal proliferation, and neoangiogenesis[227,228]) can lead to stenosis and consequent myocardial ischemia,[224,229] and even normal-appearing sites of regressed aneurysms continue to exhibit an abnormal response to experimental stimuli.[230] Large-

and giant-sized aneurysms (with rare exception[231]) do no undergo spontaneous regression.[232,233]

Thrombosis will occur in the majority of large- and giant-sized aneurysms; the highest risk for thrombosis formation is in the acute phase (within 30 days) and remains high in persisting large aneurysms.[234] The thrombotic risk associated with regressed aneurysms remains unclear.

Mechanisms of Thrombosis in Kawasaki Disease

The occurrence of marked thrombocytosis in KD was reported from the earliest case series.[1,235] (As an aside, early thrombocytopenia in KD is occasionally seen[236,237] and is associated with poorer outcomes[238]: increased risk of coronary artery aneurysms,[239,240] the Kawasaki shock syndrome,[241] and the macrophage activation syndrome.[242–244]) Platelet counts typically remain within the normal range during the acute phase, rising in the second and third week of the disease in response to high circulating thrombopoietin.[175,245,246] So-called 'reactive' or 'secondary' thrombocytosis is a normal part of the acute phase reaction, occurring in the context of infection, trauma, surgery, and chronic inflammatory states.[247] While reactive thrombocytosis has been associated with increased (venous) thrombosis risk in adults,[248] this has not been shown in children.[249] Degree of thrombocytosis has, however, been associated with the risk of IVIG non-response and development of coronary artery aneurysms.[171]

Perhaps of greater importance than thrombocytosis—especially in the very early phase of KD—is platelet activation and aggregation.[250] Platelet activating factor (PAF) and related molecules (pro-inflammatory mediators that act both on platelets and endothelial cells) are elevated in KD.[251] Indeed, platelet derived microparticles (PDMPs, endoplasmic reticulum-derived vesicles that are discharged by platelets on activation and considered markers of platelet activation) are elevated in the first few days of KD.[252] Platelet aggregation has also been demonstrated in the very early days of KD,[253] suggesting that a prothrombotic environment exists well before thrombocytosis is seen.[252]

Haemodynamic factors within aneurysms also produce favourable conditions for thrombosis. Stagnant blood with low flow velocity is classically associated with venous thrombosis, whereas arterial thrombosis is associated with platelet activation at sites of high wall shear-stress (which is why anti-platelet drugs are preferred for the prevention of arterial thrombosis).[254] Coronary aneurysms seen in KD demonstrate both of these factors, with regions of low flow velocity and regions of high wall shear-stress.[255–257] Indeed, currently-used approaches for thrombotic risk stratification (namely maximum aneurysm dimension as measured by transthoracic echocardiography) do not consider the haemodynamic variables most predictive of thrombus formation (namely regional peak flow velocity and wall shear stress).[256]

Efficacy of Aspirin for Thromboprophylaxis in Kawasaki Disease

While the relative risk of coronary artery thrombosis in acute KD (and especially among those with large- and giant- aneurysms) is high, the absolute risk remains low. As appropriately-powered studies would need to be prohibitively large, recommendations regarding thromboprophylaxis have largely come from expert consensus informed by extrapolation from adult data.[21]

The efficacy of aspirin for the primary prevention of coronary heart disease in adults is well established.[258–260] While COX-2 inhibition (responsible for the anti-inflammatory effects of aspirin) requires high dosing and frequent administration, COX-1 inhibition (largely responsible for the antiplatelet effects) is effective at low doses and daily administration.[261] There are a number of reasons for this: Firstly, aspirin irreversibly acetylates its target site on COX-1 with 50- to 100-times greater effectiveness than for COX-2. Secondly, while production of COX-2 in tissue cells is inducible—and acetylated COX-2 molecules can therefore be replaced, platelets lack the cellular machinery for protein synthesis—meaning that the effect of aspirin on platelets persists for the life of the platelet.[261]

Despite the population-level efficacy of aspirin for primary prevention of coronary artery disease, myocardial infarctions have occurred among individuals taking aspirin, leading to the recognition of 'aspirin resistance'.[262] While the most common reason for treatment failure is non-compliance,[262] other mechanisms are well described: other non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen) compete with aspirin to bind with COX-1 but do so reversibly; unbound aspirin is then readily metabolised and excreted.[262,263] It is also known that platelets can be activated by COX-1 independent routes (through platelet surface receptors for adenosine diphosphate [ADP], thrombin, adrenaline, collagen, and fibrinogen)—indeed these pathways seem to be enhanced in patients treated with aspirin.[262] Finally, while pharmacokinetic variability (such as inadequate dose) might be thought to result in treatment failure, this is thought to be unlikely.[262] Aspirin's inhibition of COX-1 is thought to be saturable at extremely low concentrations[262]; indeed, substantially lower doses of aspirin (50 mg daily) than are currently recommended for secondary prevention of myocardial infarction have been shown to have equivalent efficacy.[264]

As already mentioned, early attempts to utilise the anti-inflammatory effect of aspirin in KD were frustrated by difficulties in achieving expected serum salicylate concentrations despite enormous doses of aspirin.[6,193,195] Those investigators were trying to achieve serum salicylic acid concentrations of 200 mg/L, based on the observation (in an observational study by Jacobs *et al* involving 22 children with acute KD) that this was the dose at which

defervescence typically occurred.[6] The reason for this pharmacokinetic anomaly has never been identified: some investigators recovered most of the aspirin dose from the stool[265] (suggesting poor absorption), whereas others recovered significant amounts from the urine[193] (implying at least some absorption). Indeed, the validity of the estimated therapeutic threshold for aspirin's anti-inflammatory action is dubious, owing to significant methodological issues in the study. Firstly, some children in the study received corticosteroids; these are anti-inflammatory drugs in their own right, and may enhance the excretion of salicylic acid.[266] Secondly, while the elimination half-life of salicylic acid is only around four hours,[267] serum concentration was measured only daily; no detail was given as to the relative timing of aspirin administration and sample collection.[6] Moreover, the relevance of these findings to the COX-1-dependent inhibition of platelet activation is entirely unclear: the anti-platelet effects of aspirin are mediated by acetylsalicylic acid (ASA)—not salicylic acid.[268]

While the issue of aspirin resistance continues to be an area of intense research, assays to quantify the anti-platelet effect continue to give highly variable results.[269–273] Some investigators have attempted to measure platelet function in children taking aspirin for KD. Akagi *et al* found equally low concentrations of thromboxane B2 on day 4 of illness between children given aspirin at 100 mg/kg/day and those given aspirin at 30 mg/kg/day (as the production of thromboxane is dependent on COX-1, lower concentrations are thought to reflect more complete COX-1 inhibition).[195] Fulton *et al* also demonstrated equivalent thromboxane suppression in those given aspirin at 30 mg/kg/day versus 60 mg/kg/day, however the timepoint for that result is not clear.[274] At 6–8 weeks, after the aspirin dose has been reduced to 3–5 mg/kg/day, thromboxane levels were noted to have slightly increased, suggesting persisting COX-1 activity at that dose. Both of these studies measured the activity of COX-1, however as mentioned there are other pathways for platelet activation.[262] Yahata *et al* reported a significant reduction in circulating circulating PDMPs (a down-stream rather than up-stream surrogate for platelet activation) following the administration of moderate-dose aspirin in acute KD.[252] Tanoshima *et al* attempted a systematic review and meta-analysis of the effectiveness of anti-platelet therapy in KD[275]; while 20 studies were identified many were more than 20 years old or only available in Japanese. Moreover, significant methodological heterogeneity between studies precluded any analysis.

Adverse Effects and Interactions

While high rates of salicylism were observed ongoing children receiving extremely high doses of aspirin,[276] modern doses are well tolerated.[277] Kuo *et al* reported lower haemoglobin concentrations among those receiving moderate-dose aspirin than those receiving low-dose aspirin,[278] while

Kawakami *et al* reported a case of drug reaction with eosinophilia and systemic symptoms (DRESS) in a boy treated with high-dose aspirin for KD.[279]

One feared complication of aspirin use in children is Reye syndrome. Described as "encephalopathy and fatty degermation of the viscera" by Australian paediatric pathologist Dr Reye in 1963, the condition presented with encephalopathy and seizures and had a high mortality.[280,281] There was often hypoglycaemia and low CSF glucose, as well as high serum concentrations of toxic metabolites. An association with aspirin—especially with co-occurring influenza or varicella infection—was later observed,[282] leading to the use of aspirin in children being deemed contraindicated (except for use in KD).[283] Indeed, case reports exist of children presenting with Reye syndrome while taking aspirin for KD.[284] Despite widespread acceptance the causal link between aspirin and Reye syndrome was controversial.[285] Its disappearance in the decades since aspirin use in children was discontinued has been seen by some as evidence of a successful public safety intervention.[286] Others have argued that advances in the field of metabolic disorders has seen a diverse set of metabolic disorders (possibly exacerbated by aspirin, but inborne nonetheless) reclassified according to a more precise ontology.[287–290] Regardless of the true ontological status of Reye syndrome, many guidelines continue to advise against the use of aspirin for children with KD and co-occurring influenza, as well as recommending annual influenza immunisation.[21]

Clinical Practice Guidelines

Prior to 2017 the American Heart Association specifically recommended the use of high-dose aspirin in the acute phase of KD[291]; this changed with the 2017 Statement, which allowed that:

> Administration of moderate- (30–50 mg/kg/d) to high-dose (80–100 mg/kg/d) ASA is reasonable until the patient is afebrile, although there is no evidence that it reduces coronary artery aneurysms (Class IIa; Level of Evidence C).[21]

Indeed, high-dose aspirin appears to have fallen out of favour—only two of the reviewed guidelines recommend its use, and both of those pre-date the 2017 AHA Statement (**Table 2.3.1**).[32,33] Almost all of the reviewed guidelines recommend the use of moderate-dose aspirin in the acute phase of KD. Low-dose aspirin is only recommended by one Swedish guideline and two Australian guidelines.[22,23,31]

Where authors sought to quantify the level of evidence informing recommendations there appeared to be substantial variation in how the evidence was assessed. The authors of the Italian guidelines (published in 2018) suggested that their recommendation in favour of moderate-dose aspirin were based on class I evidence (meta-analyses or systematic reviews

from randomized controlled trials).[187] One year later the authors of the European consensus-based recommendations for the SHARE initiative graded the evidence for the same recommendation as 2A (controlled study without randomisation). A subsequent revision of the Italian guidelines did not attempt to quantify the quality of evidence or strength of recommendations.[26]

Table 2.3: Clinical Practice Guidelines for the Use of Aspirin in Acute Kawasaki Disease

Guideline	Aspirin Dose	When to Reduce Dose	Comment
NZ (2022)[25]	"7.5–12.5 mg/kg four times daily" (Moderate-dose)	"Once the fever is under control"	A previous version of this document recommended the same dose, but as "30-50 mg/kg/day in 4 divided doses".[292]
AU-RCH (2021)[22]	"3-5 mg/kg orally daily as a daily dose" (Low-dose)	N/A	
AU-PCH (2021)[23]	"3-5 mg/kg daily" (Low-dose)	N/A	
ACR (2021)[18]	No recommendation	N/A	The document states that "For patients with acute KD, using aspirin is **strongly** recommended over no aspirin" (emphasis from original), while grading the level of evidence for the recommendation as Very low.
ISP (2021)[26]	"...daily dosage of 30–50 mg/kg divided into 4 doses" (Moderate-dose)	After sustained defervescence for 48 hours.	The previous iteration of this guideline inexplicably graded the level of evidence for this recommendation as class I (meta-analyses or systematic reviews from randomized controlled trials) with a strength of recommendation grade A (highly recommended). The revised version does not attempt to quantify the quality of evidence or strength of recommendations.
JSPCCS (2020)[27]	"30–50 mg/kg/day, in divided doses 3 times a day" (Moderate-dose)	After sustained defervescence for 48–72 hours.	This document gives conflicting explanations for the recommended dose, and it is unclear whether a moderate dose is intended to have an anti-inflammatory effect or ensure an antiplatelet effect in the context of poor absorption.
IAP (2020)[28]	"30–50 mg/kg/day in 3-4 divided doses" (Moderate-dose)	After sustained defervescence for 48 hours.	
DGPK (2020)[29]	"30–50 mg/kg/day" (Moderate-dose)	After sustained defervescence for 48–72 hours.	
SHARE (2019)[20]	"30–50 mg/kg/day" (Moderate-dose)	"...until fever has settled for 48 h, clinical features are improving, and CRP levels are falling."	This document graded the level of evidence as 2A (controlled study without randomisation) and the strength of recommendation as C (based on level 3 or extrapolated from level 1 or 2).

Continued...

Table 2.3 continued...

Guideline	Aspirin Dose	When to Reduce Dose	Comment
AEP (2018)[30]	"30–50 mg/kg/day every 6 h, PO" (Moderate-dose)	After sustained defervescence for 48–72 hours.	This document advises to discontinue aspirin if symptoms of salicylism appear. Concomitant use of ibuprofen is discouraged due to competitive inhibition of COX-2 binding. Finally, relatively extensive advice is given for the prevention of Reye syndrome in children with concomitant influenza or varicella infection.
SW (2018)[31]	"2–5 mg/kg/day" (Low-dose)	N/A	
AU-TG (2017)[24]	No recommendation, however the use of moderate- or high-dose aspirin in the acute phase is implied.	"Once the fever has resolved"	
AHA (2017)[21]	Use of moderate- or high-dose aspirin is "reasonable"	"Until the patient is afebrile"	This document grades the level of evidence as level C (very limited populations evaluated or only consensus opinion of experts, case studies, or standard of care) and estimates the treatment effect as class IIa (benefit >> risk). The previous iteration of AHA guidelines specifically recommended high-dose aspirin without seeking to quantify the level of evidence or strength of recommendation.[291]
ASP/ASC (2016)[32]	"80–100 mg/kg/day orally (every 6 hours) ... maximum 2.5g" (High-dose)	After sustained defervescence for 72 hours.	This document (again, inexplicably) grades the level of evidence for this recommendation as level A (strong evidence, from randomized clinical trials or meta-analyses. Multiple groups of populations at risk evaluated. General consistency in the direction and magnitude of the effect) with a recommendation strength of class I (evidence and/or general agreement that the procedure or treatment is beneficial, useful, and effective).
DM (2015)[33]	"80–100 mg/kg/day divided into 4 doses" (High-dose)	After sustained defervescence for 48–72 hours.	The 2004 AHA statement is cited for this recommendation.[291]
UK (2002)[34]	"30–50 mg/kg/day in four divided doses" (Moderate-dose)	"When fever settled"	This document goes to some lengths to highlight the scant evidence with which to make a recommendation, noting only that "...it is our practice to administer aspirin at a dose of 30 mg/kg/day during the acute phase of the illness".

Conclusions

Moderate- and high-dose aspirin continues to be recommended for acute KD in most published guidelines, yet a coherent rationale for this recommendation can be harder to find. Recent Japanese guidelines, with reference to their recommendation in favour of moderate-dose aspirin in the acute phase of KD, equivocate: On the one hand they acknowledge the antiplatelet efficacy of low-dose aspirin but emphasise the need for higher doses to achieve anti-inflammatory effects. Later it is suggested that poor absorption of aspirin means that higher doses are needed for adequate antiplatelet effect.[27]

Progress in this area will be difficult without the articulation of clear and coherent principles for clinical decisions. Clinicians should state clearly what they think is being achieved by using higher doses of aspirin in KD, so that these hypotheses can be interrogated. Some may advocate moderate- or high-dose aspirin for its anti-inflammatory effect; this is unjustified. No evidence has ever been presented to suggest that children given moderate- or high-dose aspirin have better coronary outcomes than those given low-dose aspirin.[202,204,205,207–209,293,294] Moreover, if enhanced suppression of inflammation is desirable in individual cases then corticosteroids have now been shown to be both safe and (somewhat) effective—with much less pharmacokinetic uncertainty.[295–300]

Others may favour moderate- or high-dose aspirin to guarantee antiplatelet efficacy in the context of uncertain absorption in acute KD. While the science underpinning such concerns is shaky at best, such concerns are valid—perhaps especially so in Australia, where access to early echocardiography in the acute phase of the disease may be poor.[301] Yet advances in analytic techniques for quantifying antiplatelet activity are making this question increasing amenable to empirical investigation.[269,270,302–305] (The literature on thromboelastography in children with a Fontan circulation is particularly interesting and relevant in this regard.[304,305]) Indeed, Australia—where low-dose aspirin from the time of KD diagnosis is common—is well placed to contribute to such studies.

Part 4: Corticosteroids

Background

Corticosteroids have been used to suppress the systemic inflammation of acute KD since before the condition had been described. Based on their known efficacy in a range of other vasculitides, corticosteroids were used in by Japanese clinicians to treat the mucocutaneous ocular syndrome in the 1950s[306] and by American clinicians to treat infantile periarteritis nodosa in the 1960s (both of which may have been—or at least included children with—KD).[307] Indeed, many of Kawasaki's original cohort were administered corticosteroids in a range of formulations.[1]

The first trial of treatment protocols for KD was undertaken by Kato *et al* and published in *Pediatrics* in 1979.[3] As described in Section 2: Aspirin, the study comprised five arms, of which three included corticosteroids.

Protocol 1:	Prednisolone + Cephalexin (n = 17)
Protocol 2:	Prednisolone + Warfarin + Cephalexin (n = 7)
Protocol 3:	Prednisolone + Aspirin + Cephalexin (n = 7)
Protocol 4:	Aspirin + Cephalexin (n = 36)
Protocol 5:	Cephalexin alone (n = 25)

Children treated according to Protocols 1, 2, and 3 were given oral prednisolone 2–3 mg/kg/day for at least two weeks (but until resolution of clinical signs and normalisation of ESR to below 20mm/Hr), which was then weaned to 1.0–1.5 mg/kg/day for another 2 weeks. The primary outcome was coronary artery aneurysms as seen on angiography at 1–2 months after disease onset. Results of the study are shown in **Table 2.4.1**.

Table 2.4: Rate of Coronary Artery Aneurysm Formation by Treatment Protocol, Kato *et al* (1979)

Treatment Protocol	Aneurysms	
1. Prednisolone + Cephalexin	11/17	(65%)
2. Prednisolone + Warfarin + Cephalexin	2/7	(29%)
3. Prednisolone + Aspirin + Cephalexin	0/7	(0%)
4. Aspirin + Cephalexin	4/36	(11%)
5. Cephalexin	5/25	(20%)

As mentioned, these results gave rise to a paradigm whereby the use of corticosteroids in KD was contraindicated—both as primary therapy[299,308] and in the increasingly-recognised phenomenon of IVIG-resistant disease.[198,199] The findings were, however, controversial: some of Kato's contemporaries criticised the dosing of prednisolone as insufficient and the timing of corticosteroid therapy as too late.[9] To address these concerns Kijima *et al* tested a protocol consisting of high-dose (30 mg/kg/day) pulse methylprednisolone for 3 days.[9] They stratified patients with acute KD into 3

groups (E1, E2, and E3) according to the degree of involvement of the coronary arteries as seen on echocardiograms (E1: increased echo density; E2: coronary dilatation; E3: coronary aneurysm). Among children with aneurysms (E3), those in the steroid group were much more likely to have improvement of the lesions than those in the control group (50% *versus* 0%, $P < 0.005$). Improvements in E2 lesions, and the pooled data for E2+E3 lesions, did not meet the threshold for statistical significance. While the study was methodologically more rigorous than that of Kato the paper gives no details about randomisation or blinding, and little information is given about the baseline characteristics of each group.

By the time that IVIG was starting to be used for KD opinions regarding the role of corticosteroids were divided. Some worried that corticosteroids worsened coronary outcomes and felt that they were contraindicated.[198,199,299,308] Others perceived a role of corticosteroids but advocated very different protocols: Low-dose, long-course (LDLC) corticosteroids (typically involving a weaning course of oral prednisolone over several weeks) were favoured by some investigators (particularly in Japan)[297,300,309]; conversely, high-dose, short-course (HDSC) corticosteroids (typically intravenous pulse methylprednisolone, either as a single dose or over several days) were pursued elsewhere (notably—although not exclusively—in America).[56,296,299] With the efficacy of IVIG having been firmly established, all subsequent trials of corticosteroids as primary therapy for KD evaluated combined IVIG plus corticosteroid (primary adjunctive therapy) against IVIG alone (with one very recent exception[295]). Other research has assessed the value of corticosteroids for IVIG-resistant KD. Both of these roles are reviewed below.

Corticosteroids as Primary Adjunctive Therapy for Acute Kawasaki Disease

Corticosteroids as primary adjunctive therapy has been assessed in both unstratified patients[295,297,299,309] and at high risk for severe disease (defined either as risk for IVIG resistance[298,300,310,311] or the presence of aneurysms at presentation[296,312,313]). The issue has been subjected to multiple systematic reviews and meta-analyses, with at least seven published in English as of late 2022.[314–320] The most recent of these was a systematic review and meta-analysis for the Cochrane Collaboration by Green *et al* published in May 2022[320]; it was an update to an earlier Cochrane review by the same investigators published in 2017.[318] The investigators identified eight studies that met inclusion criteria, of which only one had not been included in the previous review (and that study only considered corticosteroids as secondary therapy).[321] Details of the seven studies on primary adjunctive corticosteroids are shown in **Table 2.4.2**. Studies differed in primary outcome; some assessed the incidence of coronary artery abnormalities (which was usually defined according to the Japanese

Ministry of Health criteria[*]), while others compared coronary artery z-scores between groups.

In a single-centre trial of at Boston Children's Hospital, Sundel *et al* randomised 39 patients with complete KD and normal coronary arteries to receive standard of care (IVIG 2 g/kg and high-dose aspirin) with or without HDSC corticosteroid (a single dose of intravenous methylprednisolone, given prior to the IVIG).[299] Those in the corticosteroid group had faster resolution of fever and shorter length of admission compared with those in the control group; rates of in-hospital adverse effects were similar between groups. There were no significant differences in coronary outcomes[†] at two and six weeks. HDSC corticosteroids were also assessed by Newburger *et al* in a multi-centre, randomised, double-blinded, placebo-controlled trial.[296] The study did not exclude children with incomplete KD or with coronary abnormalities at enrolment. A total of 199 children were randomised to receive IVIG with or without HDSC corticosteroid (treatments were similar to that of Sundel *et al*). Those in the corticosteroid group had a slightly shorter length of stay (although this was not clinically significant) and faster normalisation of the erythrocyte sedimentation rate (ESR[‡]) but not C-reactive protein (CRP). There were no differences between groups in terms of rate of retreatment or coronary artery abnormalities[§].

Finally, Ogata *et al* compared IVIG plus HDSC corticosteroid to IVIG alone in a single-centre Japanese trial.[56] They enrolled children at high risk for treatment failure[**] but without coronary involvement at diagnosis, randomising them to receive standard of care (IVIG 2 g/kg plus moderate-dose aspirin) with or without a single dose of intravenous pulse methylprednisolone (30 mg/kg) prior to IVIG (those in the corticosteroid group were also maintained on a heparin infusion for the first 24 hours of therapy[††]). Coronary artery z-scores were higher for those in the control group

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[*] The Japanese Ministry of Health criteria define a coronary artery abnormality by the observation of any of the following: i) a luminal diameter >3.0 mm (age <5 years) or >4.0 mm (age ≥5 years); ii) an artery segment with a luminal diameter ≥1.5 times that of an adjacent segment; iii) a luminal contour that is clearly irregular.[322]

[†] While Sundel *et al* indicated that they assessed coronary arteries using both the Japanese Ministry of Health criteria and by normalised dimensions (i.e., z-score), only the latter was reported.

[‡] It should be noted that ESR is an unreliable marker of inflammation after the administration of IVIG due to the net-positive charge of globulins at physiological pH, which promotes rouleaux formation.[323–325]

[§] Newburger *et al* defined coronary artery abnormality either according to the Japanese Ministry of Health criteria or a luminal z-score of ≥2.5 in either the proximal left anterior descending coronary artery or the proximal right coronary artery.

[**] Based on an Egami score[46] ≥3.

[††] No explanation for the use of heparin—or why it is only given to those in the corticosteroid group—is given in this paper.

than those in the corticosteroid group: the difference was statistically different at 36 hours for the left and right main coronary arteries, and at 1 month for the left main coronary artery. An included boxplot* is more evocative, indicating very large differences in the relative frequency of moderate and large aneurysms in all vessels at both timepoints. While the investigators do refer to this in the text—noting that aneurysms with a z-score ≥2.5 were observed in 9% of those in the corticosteroid group compared with 39% of those in the control group at 1 month (P = 0.04)—the observation is not discussed at length.

Ogata *et al* also reported greater improvement in markers of inflammation at 36 hours among those in the corticosteroid group than in the control group (including lower neutrophil count and fraction, lower CRP, and higher albumin—all of which were statistically significant), as well as shorter duration of fever and lower rates of retreatment in the corticosteroid group.[56] Conversely, those in the corticosteroid group had higher rates of adverse events than those in the control group. Unfortunately, the use of heparin only in the corticosteroid group confounds the interpretation of these findings. Heparin has intrinsic anti-inflammatory activity,[326,327] which may explain some of the findings of this study. Additionally, this may have contributed to the higher rates of adverse events in that group.

Most studies of primary adjunctive corticosteroids in Japan have assessed LDLC corticosteroid protocols. In a multi-centre trial conducted in the Gunma Prefecture of Japan, Okada *et al* randomised 32 patients with complete KD to receive standard of care (IVIG 1 g/kg/day for 2 days plus moderate-dose aspirin and dipyridamole) with or without LDLC corticosteroids.[309] Those in the corticosteroid group were given intravenous prednisolone 2 mg/kg/day until defervescence, then oral prednisolone at the same dose until the CRP had normalised; the dose of prednisolone was then weaned over a period of 10 days. Inflammatory cytokines (IL-2, IL-6, IL-8, and IL-10) were all significantly higher in the control group then the corticosteroid group immediately post-treatment, however the difference was not seen 1 week (for IL-2 and IL-8) or 2 weeks (for any of the cytokines); CRP was also slower to normalise and the duration of fever was longer in the control group compared with the corticosteroid group. No coronary artery abnormalities† were observed in any child.

Inoue *et al* performed a very similar study—also in Gunma Prefecture, with the same investigators and with an overlapping study period—in which children with aneurysms at enrolment were excluded.[297] One hundred and

* Figure 2 of Ogata *et al*.[56]

† Okada *et al* defined coronary artery abnormality according to the Japanese Ministry of Health criteria.

seventy-eight children were randomised to receive standard of care with or without LDLC corticosteroids (the only difference being a slightly slower wean in the dose of prednisolone compared with Okada *et al*).[297] Rates of coronary artery abnormalities* were lower in the corticosteroid group than in the control group (2% *versus* 11%, $P = 0.017$) before one month, but not at one month (0% *versus* 3%, $P = 0.119$). Rates of treatment failure were significantly lower in the corticosteroid group compared with the control group (6% *versus* 18%, $P = 0.01$).

The most anticipated trial of primary adjunctive corticosteroids for acute KD was the RAISE study, conducted by Kobayashi *et al*.[300] This was a large multi-centre (74 recruitment sites throughout Japan), randomised, open-label trial of primary adjunctive corticosteroids for children deemed to be at high risk for IVIG resistance† but without aneurysms at enrolment.[45] 242 children were randomly assigned to receive standard of care (IVIG 2 g/kg plus aspirin 30 mg/kg/day) with or without LDLC corticosteroids (the corticosteroid protocol was very similar to that of Inoue *et al* and Okada *et al*). Echocardiograms were performed at enrolment (to determine eligibility) and then at weeks 1, 2, and 4. The primary endpoint was incidence of coronary artery abnormalities‡ at any timepoint, secondary outcomes included coronary artery abnormalities at 4 weeks, coronary artery z-scores, rate of retreatment, duration of fever, CRP at weeks 1 and 2, and rates of serious adverse events. The study was terminated early due to significantly lower rates of coronary artery abnormalities in the corticosteroid group compared with the control group. The relative risk for coronary artery abnormalities at any timepoint in the corticosteroid group versus the control group was 0.2 (95% CI 0.12–0.28), with the number needed to treat to prevent one occurrence of coronary artery abnormality estimated to be five. For abnormalities at 4 weeks the relative risk was 0.09 (95% CI 0.02–0.16), with an estimated number needed to treat of ten. Coronary artery z-scores were lower in the corticosteroid group for every vessel at every timepoint. The investigators report that only one patient (in the control group) had a giant aneurysm (defined in absolute terms) of the left anterior descending artery, yet an included boxplot§ indicates that there were 3 individuals with right coronary artery z-scores greater than 10 (one in the corticosteroid group and two in the control group, timepoint of measurement not given). Data on the relative incidence of aneurysms by severity are not provided.

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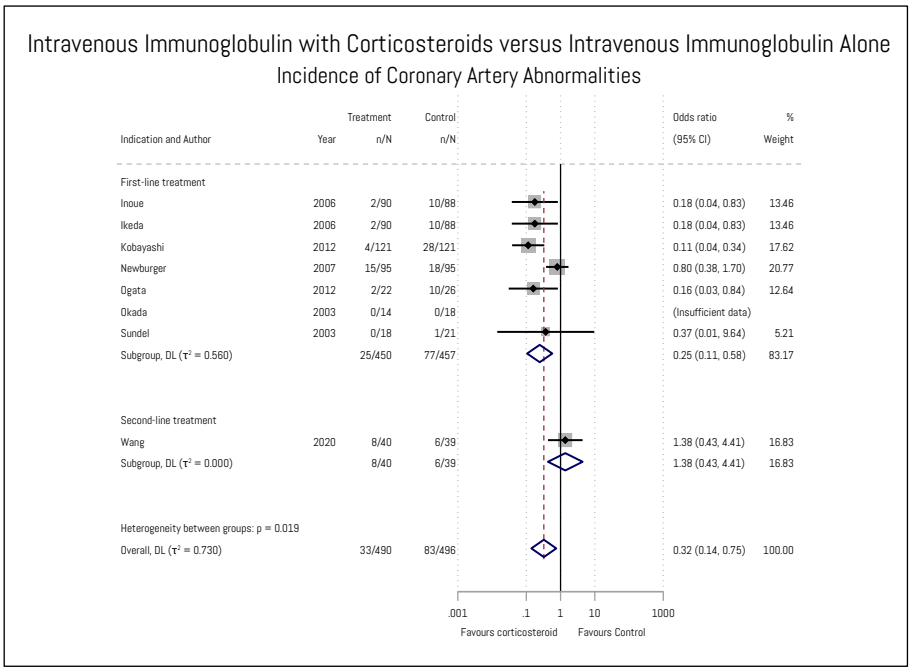
* Inoue *et al* defined coronary artery abnormality according to the Japanese Ministry of Health criteria.

† Based on a Kobayashi score[45] ≥5.

‡ Kobayashi *et al* defined coronary artery abnormality according to the Japanese Ministry of Health criteria.

§ Figure 2 of Kobayashi *et al*.[300]

Figure 2.2: Original forest plot from Green *et al*.



In their pooled analysis of the aforementioned studies (**Figure 2.4.1**), Green *et al* reported a pooled odds ratio for coronary artery abnormalities in favour of primary adjunctive corticosteroids (OR 0.25, 95% CI 0.10 to 0.58),[320] however methodological issues biased the result in favour of corticosteroids. Green *et al* included an abstract (Ikeda *et al*[328]) by the same research group responsible for the paper by Inoue *et al*. Both report a study at the same institution, at the same time, using the same research ethics approval, and with the same number of patients in each group (90 in the steroid group and 88 in the control group). Inoue *et al* describes the use of a severity score in their Methods, but the results are not stratified by that variable. By contrast, Ikeda *et al* only report results by severity strata. Outcome statistics given for both of these studies in the meta-analysis are identical. It seems highly likely that these publications describe the same cohort and represent duplicate data. Indeed, while Ikeda *et al* was included in this and the previous Cochrane review,[318] it was not included in any other meta-analysis on the topic.[314–317,319]

There is also significant unrecognised heterogeneity with regard to the outcome measure selected for inclusion in the meta-analysis. Three studies defined coronary artery abnormality according to the unmodified Japanese Ministry of Health criteria (Okada *et al*[309*], Inoue *et al*[297], and Kobayashi *et al*[300]), while two used luminal z-score alone (Sundel *et al*: z-score >3,[299] Ogata *et al*: z-score ≥2.5[56]), and one used a combination of the two (Newburger *et al*: Japanese Ministry of Health criteria or z-score ≥2.5 in either the LAD or RMCA). While it isn't clear that this introduced systematic bias, heterogeneity in the outcome timepoint did: most studies reported the rate of coronary

[*] As no coronary abnormalities were observed in Okada *et al*, the study did not contribute to the estimated treatment effect size.

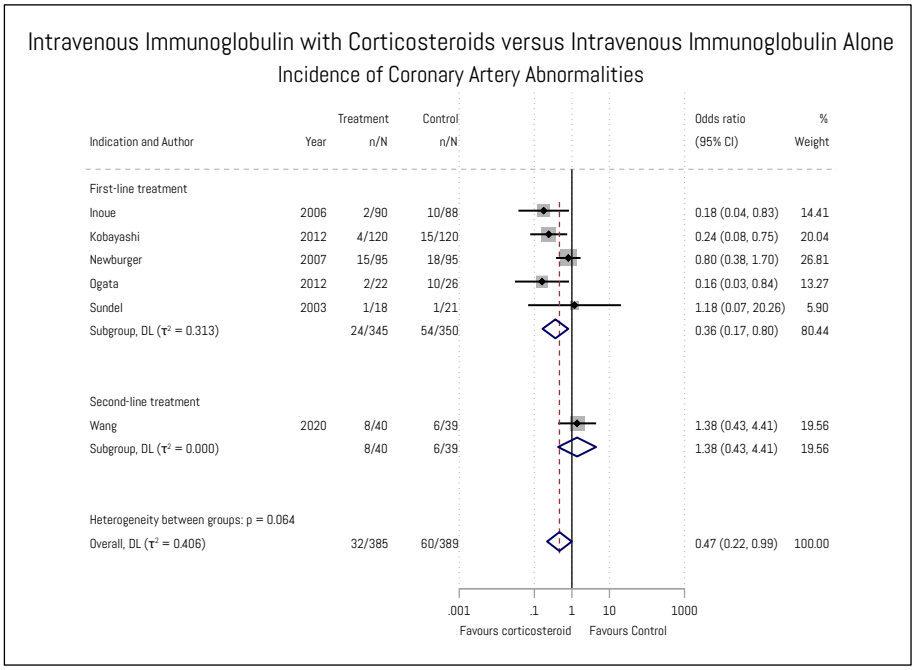


Figure 2.3:
Updated forest plot. Ikeda *et al* has been removed, and all data refer to a single timepoint between 4 and 6 weeks after illness onset.

artery abnormalities at around 4 weeks, however Sundel *et al* measured the outcome at 2 and 6 weeks[299]; the former was used in the meta-analysis. More significantly, while Kobayashi *et al* reported the rate of coronary artery abnormalities at 4 weeks as a secondary outcome (RR 0.09, 95% CI 0.02–0.16), their primary outcome was rate of coronary artery abnormalities at *any* timepoint (weeks 1, 2, and 4; RR 0.20, 95% CI 0.12–0.28)—a significantly larger effect size. Green *et al* used the latter in their meta-analysis, further biasing their result in favour of corticosteroids. When these issues are considered the new pooled effect size remains significant (**Figure 2.4.2**), but is smaller (OR 0.36, 95% CI 0.17 to 0.80).

Subgroup analysis did reveal additional nuances: Confidence intervals for the odds ratio in favour of steroids (for the prevention of coronary artery abnormalities) excluded 1 in all Japanese trials but no American trials. The reason for this is unclear but may relate to the use of pulse methylprednisolone favoured in American trials, or the selection of higher-risk patients favoured in Japanese trials.

The data available to evaluate primary adjunctive corticosteroids are lacking in several ways. Most studies reported the relative frequency of any coronary abnormalities,[56,296,297] some reported group differences in coronary artery z-scores[56,296,299,300], while one study reported no coronary abnormalities in either group.[309] Only one study gave details on the relative frequency of coronary dilatation stratified by magnitude.[299] Data showing a reduction in group coronary artery z-scores are compelling (particularly those from Kobayashi *et al*[300]), however the clinical relevance of that outcome is not clear. Dilated (but not aneurysmal) coronary arteries are commonly observed in acute KD,[222,233,329] and have also been reported in children with systemic

inflammation not caused by KD.[330–332] The vast majority of these 'lesions' resolve[222,223,333,334]; indeed, coronary dilatation may represent a heterogenous group of phenomena—many of which lack aneurysmal potential.[335] Technical challenges in coronary measurement, as well as methodological challenges underpinning their parametric normalisation, can result in high variability in z-scores.[336*] Occasionally, coronary arteries with 'normal' z-scores in the acute phase of KD demonstrate a reduction in calibre at follow-up, suggesting that they had been 'functionally' dilated.[329] Other vessels may have 'high' z-scores in the acute phase with no change in calibre over time; this may be consistent with a dominant coronary artery branch.[335†] Small and moderate coronary aneurysms can also follow a very different natural history to large and giant aneurysms, with logarithmic regression over time being the norm.[223,226,329,335‡] Further, while current recommendations focus on maximum calibre to estimate the risk of coronary abnormalities,[21] this is not a strong predictor of subsequent thrombosis (which is much more heavily influenced by haemodynamic consequences of disturbed vessel morphology).[255–257] Indeed, an over-reliance on coronary z-scores (particularly those representing only 'dilatation', and especially at early follow-up) are likely to significantly overestimate disease risk in KD.[333] It follows that statistically significant yet small differences in coronary z-scores between groups is likely to result in over-estimation of the likelihood of treatment effect, while providing little information regarding effect size. Future studies should be designed and reported with clinically important outcomes in mind so that meaningful absolute and relative treatment effect sizes can be determined.[341–344§]

Some of these issues were addressed by Kobayashi *et al.*[300] That was the only study to estimate the number needed to treat for the prevention of coronary artery abnormalities,[300] yet the inclusion criteria limit the utility of the results outside of Japan. The Kobayashi score used to define the 'at risk' population for the study demonstrates poor accuracy (especially low sensitivity) for predicting IVIG resistance in a number of populations outside of Japan.[50,345–350] Additionally, the exclusion of children with coronary abnormalities at diagnosis meant that the cohort (children with KD at high risk for IVIG resistance but without any coronary abnormalities—more than three quarters

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[*] The dimensions of the left main coronary artery demonstrate particularly high variability[26,336]; consequently, this vessel is excluded in some analyses.[226]

[†] Importantly, patterns of coronary dominance differ between populations,[337–339] which may not have been reflected in the populations used for parametric normalisation.

[‡] Note that 'regression' does not imply 'normalisation'. Aneurysmal vessels that have undergone regression (and which may appear normal on luminography) continue to show intimal thickening and abnormal response to intraluminal dipyridamole.[221,225,230,233,335,340]

[§] This would ideally be presented as, for example: the number needed to treat to prevent one high-risk coronary aneurysm (appropriately defined) at 6 months.

of whom were diagnosed on or before day 5 of illness) is not representative of the range of children for whom clinicians might be considering primary adjunctive corticosteroids.

The exclusion of children with coronary artery abnormalities at enrolment in many of these trials is of particular importance. Ever since the original trial by Kato *et al* suggested a possible negative effect of corticosteroids on coronary outcomes,[3] several investigators have questioned if corticosteroids might interrupt the normal regression of coronary lesions in the sub-acute and convalescent phase of KD.[351,352] Most evidence for this hypothesis has come from retrospective studies at high risk for selection bias[351,352], with some theoretical support from animal studies[353]; other studies have suggested enhanced aneurysm regression in those treated with adjuvant corticosteroids.[312,313] While some prospective trials have included children with aneurysms at enrolment their numbers have remained small.[296,309] Future studies should seek to address this by enrolling patients regardless of coronary status and evaluating outcomes both as strata of initial coronary status and as change from initial coronary status.

Finally, while LDLC corticosteroid protocols outperformed HDSC protocols in this meta-analysis, they can reasonably be expected to entail additional costs. These were unquantified, but might include:

1. Increased medication complexity (the need for incremental weaning of corticosteroid doses).
2. Increased patient discomfort (the need for repeated venepuncture to monitor inflammatory markers).
3. Increased patient inconvenience (the presumed need for additional outpatient visits to facilitate 1 and 2).
4. Increased healthcare costs (all of the resources utilised for 1, 2, and 3).

Any attempt to evaluate competing therapies must consider their relative costs—both in terms of resource utilisation at the health service level, and discomfort and inconvenience at the individual patient level.[354,355]

Table 2.5: Randomised, Controlled Trials of Corticosteroids as Primary Therapy in Acute Kawasaki Disease

Reference	Location & Study Design	Intervention	Control	Outcomes
Sundel (2003)[299]	USA, single-centre. Randomised treatment allocation. Inclusion: – Fever ≤10 days, and – ≥4/5 AHA criteria Exclusion: – Previous KD – Aneurysms at enrolment – Possible infection – Contraindication to steroids Blinded outcome assessment.	(*N* = 18) IVMP 30 mg/kg over 3 hours before IVIG; **PLUS:** IVIG 2 g/kg over 10 hours; **PLUS:** ASA 80–100 mg/kg/day in 4 divided doses until defervescence.	(*N* = 21) IVIG 2 g/kg over 10 hours; **PLUS:** ASA 80–100 mg/kg/day in 4 divided doses until defervescence.	Coronary artery dimensions on days 0, 14, and 42 of illness. Inflammatory markers on days 0, 14, and 42 of illness. Duration of fever.
Okada (2003)[309]	Japan, multi-centre. Randomised treatment allocation. Inclusion: – ≥5/6 Japanese criteria Exclusion: – Fever ≤9 days Unclear is assessment blinded.	(*N* = 14) IVPSL 2 mg/kg/day in 3 divided doses until defervescence, then: OPSL 2 mg/kg/day in 3 divided doses until CRP normalised, then: OPSL 2 mg/kg/day in 2 divided doses for 5 days, then: OPSL 0.5 mg/kg/day daily for 5 days; **PLUS:** IVIG 1 g/kg/day for 2 days; **PLUS:** ASA 30 mg/kg/day; **PLUS:** DPA 2 mg/kg/day.	(*N* = 18) IVIG 1 g/kg/day for 2 days; **PLUS:** ASA 30 mg/kg/day; **PLUS:** DPA 2 mg/kg/day.	Coronary artery dimensions on the day of enrolment and on days 6–8, 12–16, and 25–30 of illness. Blood parameters, with cytokines measured before and after treatment. Duration of fever.

Continued...

Table 2.5 continued...

Reference	Location & Study Design	Intervention	Control	Outcomes
Inoue (2006)[297]	Japan, multi-centre. Randomised treatment allocation. Inclusion: – ≥5/6 Japanese criteria Exclusion: – Previous KD – Aneurysm at enrolment – Fever >9 days Non-blinded outcome assessment.	(*N* = 90) IVPSL 2 mg/kg/day in 3 divided doses (the first dose preceded IVIG) until defervescence, then: OPSL 2 mg/kg/day in 3 divided doses until CRP <5 mg/L, then: OPSL 2 mg/kg/day for 5 days, then: OPSL 1 mg/kg/day for 5 days, then: OPSL 0.5 mg/kg/day daily for 5 days; **PLUS:** IVIG 1 g/kg/day for 2 days; **PLUS:** ASA 30 mg/kg/day; **PLUS:** DPA 2 mg/kg/day.	(*N* =88) IVIG 1 g/kg/day for 2 days; **PLUS:** ASA 30 mg/kg/day; **PLUS:** DPA 2 mg/kg/day.	Coronary artery dimensions on the day of enrolment and on days 6–8, 12–16, 18–22, and 25–30 of illness. Duration of fever. Time to normalisation of CRP. Rate of retreatment.
Ikeda (2006)[328] (Available in abstract form only)	Japan, number of centres unclear. Randomised treatment allocation. Inclusion and exclusion criteria unknown. Blinding unknown.	(*N* = 90) PSL (dose and route unknown); **PLUS:** IVIG (dose unknown)	(*N* = 88) IVIG (dose unknown)	Coronary artery abnormalities (no details given). Rate of retreatment.

Continued...

Table 2.5 continued...

Reference	Location & Study Design	Intervention	Control	Outcomes
Newburger (2007)[296]	USA, multi-centre. Randomised and blinded treatment allocation. Inclusion: – Day 4–10 of fever, and: – ≥4/5 AHA criteria, OR: – Coronary z-score ≥2.5 in LAD or proximal RCA, and ≥2/5 criteria (<6 months) or ≥3/5 criteria (≥6 months) OR: – Coronary aneurysm, and ≥1/5 AHA criteria. Exclusion: – Contraindication to any treatment. – Previous IVIG or steroid. – Previous KD. Blinded outcome assessment.	(*N* = 101) IVMP 30 mg/kg over 2–3 hours; **THEN:** Diphenhydramine 1 mg/kg; **PLUS:** IVIG 2 g/kg over 10 hours **PLUS:** ASA 80–100 mg/kg/day until 48 hours after defervescence	(*N* = 98) Placebo infusion over 2–3 hours; **THEN:** Diphenhydramine 1 mg/kg; **PLUS:** IVIG 2 g/kg over 10 hours **PLUS:** ASA 80–100 mg/kg/day until 48 hours after defervescence	Coronary artery dimensions at enrolment and days 7 and 36. Blood parameters at enrolment and days 7 and 36. Duration of fever. Rate of retreatment.
Ogata (2012)[56]	Japan, single-centre. Randomised treatment allocation. Inclusion: – ≥5/6 Japanese criteria, and – Egami score ≥3 Exclusion: – Previous KD – Coronary abnormality at enrolment – Given steroids before KD diagnosis Blinded outcome assessment.	(*N* = 22) Heparin 10 U/kg/hour over 24 hours; AND: IVMP 30 mg/kg/dose over 2 hours; THEN: IVIG 2 g/kg over 24 hours; AND: ASA 30 mg/kg/day to defervescence	(*N* = 26) IVIG 2 g/kg over 24 hours; AND: ASA 30 mg/kg/day to defervescence	Coronary artery dimensions before treatment and at 36 hours and 1 months after treatment. Blood parameters before treatment and at 36 hours and 1 months after treatment. Duration of fever. Rate of retreatment.

Continued...

Table 2.5 continued...

Reference	Location & Study Design	Intervention	Control	Outcomes
Kobayashi (2012)[300]	Japan, multi-centre. Randomised treatment allocation. Inclusion: – ≥5/6 Japanese criteria, and – Kobayashi score ≥5 Exclusion: – Fever ≥9 days – Coronary abnormality at enrolment – Afebrile at enrolment – Steroids in last 30 days – IVIG in last 180 days – Suspected infection Blinded outcome assessment.	(*N* = 121) IVPSL 2 mg/kg/day in 3 divided doses for 5 days or defervescence (whichever was later), **THEN:** OPSL 2 mg/kg/day in 3 divided doses until CRP ≤5 mg/L, **THEN:** OPSL 1 mg/kg/day for 5 days, **THEN:** OPSL 0.5 mg/kg/day for 5 days; **AND:** IVIG 2 g/kg over 24 hours; **AND:** ASA 30 mg/kg/day until defervescence; **AND:** Famotidine 0.5 mg/kg/day until PSL discontinued.	(*N* = 121) IVIG 2 g/kg over 24 hours; **AND:** ASA 30 mg/kg/day until defervescence.	Coronary artery dimensions at enrolment and weeks 1, 2, and 4 after enrolment. Rate of retreatment. Duration of fever. CRP at weeks 1 and 2 after enrolment.
Aslani (2022)[295] (Not included in Green *et al*)	Iran, single-centre. Randomised treatment allocation. Inclusion: – AHA criteria for complete or incomplete KD – Age 6 months to 5 years Exclusion: – 'Atypical' KD – MAS – Previous KD – Pre-existing coronary abnormality – Congestive heart failure – Chronic kidney disease – Recent steroid use – Contraindication to steroids	(*N* = 20) IVMP 30 mg/kg/day for 3 days; **THEN:** OPSL 1 mg/kg/day for 3 days; **AND:** Aspirin (dose not given).	(*N* = 21) IVIG 2 g/kg; **AND:** Aspirin (dose not given)	Coronary dimensions on day 1 (day of diagnosis), and at 2 and 8 weeks. Duration of fever.

AHA criteria, American Heart Association criteria (oro-mucosal inflammation, bilateral non-exudative conjunctival injection, polymorphous rash, extremity changes, and cervical lymphadenopathy); ASA, aspirin; CRP, C-reactive protein; DPA, dipyridamole; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; IVPSL, intravenous prednisolone; Japanese criteria (fever >38.0°C, bilateral non-exudative conjunctival injection; oro-pharyngeal inflammation, extremity changes, rash, and cervical lymphadenopathy); LAD, left anterior descending coronary artery; MAS, macrophage activation syndrome; OPSL, oral prednisolone; RCA, right coronary artery.

Corticosteroids Alone as Primary Therapy for Acute Kawasaki Disease

While Kijima *et al* had demonstrated promising results in their small trial assessing standard of care* with or without HDSC corticosteroids,[9] no subsequent trials had evaluated corticosteroids alone in acute KD. That changed in 2022 when, less than one month after the publication of the meta-analysis by Green *et al*, Aslani *et al* published the results of a single-centre, single-blinded, randomised control trial of corticosteroids alone for acute KD (study details are included in **Table 2.4.2** for comparison).[295] The study, though small, is of great interest as it represents the only head-to-head trial comparing IVIG and corticosteroid ever published.† Forty-one children with acute KD were randomly allocated to receive standard of care (IVIG 2 g/kg plus aspirin) or HDSC corticosteroid (intravenous methylprednisolone 30 mg/kg/day for 3 days, then oral prednisolone 1 mg/kg/day for 3 days) as monotherapy. The rationale for the study was to establish an evidence base for the management of KD in resource-poor settings where IVIG may not be available.[110] The authors reported lower rates of coronary artery abnormalities in the steroid group compared with the IVIG group at 2 weeks (20% *versus* 50%‡) but not at 8 weeks (5% in each group). The authors present a breakdown of coronary outcomes by lesion size at each of the timepoints, reproduced in **Table 2.4.3**.

Table 2.6: Methylprednisolone versus Intravenous Immunoglobulin as Primary Therapy for Acute Kawasaki Disease: Coronary Outcomes at Three Time Points (taken from Aslani, *et al*)

Vessel Abnormality	IVIG *N* = 20	Corticosteroid *N* = 20	*P*
At Diagnosis			
Ectasia	14 (70%)	9 (45%)	
Small aneurysm	0 (0%)	0 (0%)	0.053
Moderate aneurysm	0 (0%)	0 (0%)	
Giant aneurysm	1 (5%)	0 (0%)	
Total	15 (75%)	9 (45%)	
2 Weeks			
Ectasia	9 (45%)	3 (15%)	
Small aneurysm	0 (0%)	0 (0%)	0.047
Moderate aneurysm	1 (5%)	1 (5%)	
Giant aneurysm	0 (0%)	0 (0%)	
Total	10 (50%)	4 (20%)	
8 Weeks			
Ectasia	0 (0%)	0 (0%)	
Small aneurysm	1 (5%)	1 (5%)	0.7
Moderate aneurysm	0 (0%)	0 (0%)	
Giant aneurysm	0 (0%)	0 (0%)	
Total	1 (5%)	1 (5%)	

One child in the IVIG group was lost to follow-up. IVIG, intravenous immunoglobulin.

* Standard of care at that time being aspirin plus heparin.
† At least in the available English-language literature.
‡ The significance of this finding was not presented in the paper, but is readily calculated: $\chi 2 = 3.956$, $P = 0.047$.

The study was underpowered to demonstrate the non-inferiority of HDSC corticosteroids as compared with IVIG,[*] as such these data cannot be used to guide treatment decisions. They do, however, deserve to be replicated in larger trials. Due to the clear efficacy of IVIG in acute KD, comparative trials of other potential treatments have been deemed unethical.[358] When an effective (if not curative) treatment is available, its denial in order to test an unproven alternative is ethically problematic; but to imagine this a categorical imperative is to ignore the potential harms if effective alternatives are not pursued.

As discussed in Section 2: Intravenous Immunoglobulin, IVIG is expensive and will remain so.[110] In a study assessing cost implications of treating Guillain Barre Syndrome with plasma exchange compared with IVIG in India, Maheshwari *et al* costed IVIG at ₹1530/gram in 2018.[359] The cost of IVIG for KD in a small child is therefore prohibitive: A 12 kg child requires 24 grams of IVIG, at a cost of ₹36 720[†]—close to the median household family income.[‡] In India these are often out-of-pocket costs borne by a child's family.[359]

There are other reasons to pursue viable alternatives to IVIG as primary therapy for KD. In a 2002 recommended guideline for KD in the United Kingdom, Brogan *et al* noted their use of corticosteroids for patients who refuse IVIG on religious grounds (i.e., Jehovah's Witnesses).[34] As medical researchers we should seek to generate an evidence base that supports resilient and equitable access to effective therapies.

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[*] Sample-size calculations for non-inferiority trials with binary outcomes are complex, however the following (taken from sealedenvelope.com[356]) will suffice:

$$N = f(\alpha, \beta) \times \frac{\pi_s(100 - \pi_s) + \pi_e(100 - \pi_e)}{(\pi_s - \pi_e - \Delta)^2}$$

Where π_s and π_e are the estimated rates of events in the standard and experimental treatment group respectively, α is the significance level, β is the power, Δ is the non-inferiority limit, and

$$f(\alpha, \beta) = [\phi^{-1}(\alpha) + \phi^{-1}(\beta)]^2$$

Where ϕ^{-1} is the cumulative distribution function of a standardised normal deviate. If we take as our endpoint the proportion of patients with at least one coronary artery z-max ≥5 at 12 weeks follow-up, then we can refer to Ogata *et al*[14] to provide our estimate for the event rate among those given IVIG (roughly 6%). Assuming 90% power, 5% significance, and a non-inferiority limit of 10%, the sample-size required is 97 in each group. Given the extensive evidence on coronary outcomes with IVIG alone, the application of Bayesian methods[357] and asymmetric trial design may reduce this number.

[†] A course of intravenous methylprednisolone (1 gram for 3 doses at 30 mg/kg) can be up to three orders of magnitude cheaper.

[‡] Median annual household income in India was estimated at ₹13 860 in 2011–12,[360] and ₹44 901 in 2018.[361]

Adverse Effects and Interactions

While the short-term use of corticosteroids in children is generally well tolerated,[362,363] the protocols frequently used for acute KD are associated with a number of potential adverse outcomes.[144,364]

Avascular Necrosis

Avascular necrosis (AVN)* is a condition whereby abnormal bone vasculature results in infarction of bone and bone marrow with subsequent bony destruction.[365] While the association between exogenous corticosteroids and AVN has been recognised for over 60 years[366] the mechanism of this effect is incompletely understood.[367–369] The epiphyses and metaphyses of growing long bones are at highest risk due to high metabolic activity and vulnerable vascular supply.[367] The femoral head is by far the most common site for AVN, however the condition can affect all long and short bones—including the humeral,[366] radial,[370] and metacarpal heads,[371] the talus,[372] and the vertebrae.[373] Corticosteroids are thought to cause AVN via transient hyperlipidaemia, with circulating fat globules occluding the fine vessels of the epiphysis.[367–369] While higher rates of AVN are associated with higher daily doses of corticosteroid,[374] little else is known regarding predisposing factors for children with KD.

Psychiatric Effects

The use of corticosteroids has been associated with a range of adverse psychiatric effects in children, including disordered sleep, inattention, mood swings (with irritability and aggression commonly seen) and (rarely[375]) psychosis.[376,377] While there is a dose-response relationship, adverse effects are well documented at prednisolone doses in the 1–2 mg/kg/day range, and can occur at any time during the treatment course (but are commonly seen in the first few days).[375,378] These effects (including psychosis) typically resolve after discontinuation of corticosteroids.[375,376]

Other Adverse Effects

Bradycardia is a well-recognised effect of short courses of corticosteroids and has been observed in children with KD, however it rarely requires intervention.[379,380] Adrenal suppression also occurs, and can in rare cases precipitate an adrenal crisis.[381] Finally, while long-term treatment with corticosteroids is associated with an increased risk of opportunistic infections, this does not appear to be a significant concern with short courses, as used in KD.[362]

Clinical Practice Guidelines

Recommendations for the use of corticosteroids in KD from Clinical Practice Guidelines (CPGs) are shown in **Table 2.4.4**. There are significant differences

* Other names for this condition include *aseptic necrosis* and *osteochondritis desiccans*.

in how CPGs discuss the use of corticosteroids, with their role as primary adjunctive therapy or as secondary therapy considered in most documents. As discussed, two broad principles of corticosteroid use have been studied in KD trials—HDSC and LDLC. Most CPDs discussed protocols that fit into one of those categories, however a number of CPDs recommended protocols that combine high-dose pulsed intravenous corticosteroids followed by a weaning oral course over several weeks.[20,26]

A number of CPDs addressed the difficulty in generalising from Japanese trials due to their frequent use of severity scores, which have poor performance outside of Japan. Common indicators of severe disease that are highlighted include young age (<12 months), signs of shock, the presence of coronary abnormalities at diagnosis, and rare consequences of systemic inflammation such as macrophage activation syndrome (MAS) / haemophagocytic lymphohistiocytosis (HLH). These would seem to describe a different cohort than is identified by the Japanese risk scores (such as the Kobayashi score).

Table 2.7: Clinical Practice Guidelines for the Use of Corticosteroids in Kawasaki Disease

Guideline	Primary Adjunctive Therapy	Treatment of IVIG Resistance	Comment
NZ (2022)[25]	No recommendation	In cases of continuing treatment failure following a second course of IVIG, either HDSC or LDLC corticosteroids can be used.	Recommended only after a second course of IVIG. Also mentioned: IFX 5 mg/kg as a single dose
AU-RCH (2021)[22]	For "high risk" patients: (OPSL 2mg/kg (max 60mg) daily for a minimum of 5 days and until CRP normalises.	No recommendation	The document states that primary adjunctive corticosteroids are: "More likely to be beneficial at the commencement of treatment for KD in high risk patients, rather than after a failure of initial IVIg treatment." "High risk" is defined as: – Signs of shock. – Patients < 12 months of age. – Asian ethnicity – ALT > 100 IU/L Albumin < 30 g/L – Any patient with evidence of cardiac involvement on echocardiography at time of presentation.
AU-PCH (2021)[23]	No recommendation	No recommendation	
ACR (2021)[18]	No recommendation	Second course of IVIG is preferred, however either HDSC or LDLC corticosteroids are acceptable alternatives.	
ISP (2021)[26]	For "high risk" patients: Single dose of IVMP 30 mg/kg	IVMP 30 mg/kg/day for 3 days; THEN: OPSL 2 mg/kg/day, gradually tapered.	"High risk" is defined as: – Age <12 months – CRP >200 mg/L – Severe anaemia at disease onset – Albumin <2.5 g/dL – Liver disease – Overt coronary artery aneurysms – Macrophage activation syndrome – Septic shock

Continued...

Table 2.7 continued...

Guideline	Primary Adjunctive Therapy	Treatment of IVIG Resistance	Comment
JSPCCS (2020)[27]	For "high risk" patients: Preferred protocol (covered by insurance in Japan) is: LDLC as per RAISE protocol (see **Table 2.4.2**) Alternatively (not covered by insurance): HDSC with IVMP.	LDLC as per RAISE protocol (see **Table 2.4.2**).	"High risk" is defined as a Kobayashi score of ≥5.
IAP (2020)[28]	OPSL 2 mg/kg/day gradually tapered over 15 days after normalization of CRP levels (specific indication note given).	Discussed, but no recommendation.	
DGPK (2020)[29]	For "high risk" patients: LDLC corticosteroid.	LDLC corticosteroid with second dose IVIG HDSC given as an option in subsequent treatment failure.	"High risk" is defined as: – Age <1 year – Coronary abnormality (Z-score >2) – Severed disease (MAS, shock).
SHARE (2019)[20]	For "high risk" patients: Regimen 1: IVMP 0.8 mg/kg BD for 5–7 days or until CRP normalises; then OPSL 2 mg/kg/day and wean off over next 2–3 weeks. Regimen 2: IVMP 10–30 mg/kg (max 1g/day) daily for 3 days, then OPSL 2 mg/kg per day until day 7 or CRP normalises; then wean over next 2–3 weeks.	Regimen 1: IVMP 0.8 mg/kg BD for 5–7 days or until CRP normalises; then OPSL 2 mg/kg/day and wean off over next 2–3 weeks. Regimen 2: IVMP 10–30 mg/kg (max 1g/day) daily for 3 days, then OPSL 2 mg/kg per day until day 7 or CRP normalises; then wean over next 2–3 weeks.	"High risk" is defined as: – Kobayashi score ≥5 – Features of HLH – Features of shock – Age <1 year – Coronary and/or peripheral aneurysms.
AEP (2018)[30]	No recommendation.	Discussed, but no recommendation. Second dose of IVIG is preferred.	
SW (2018)[31]	In "high risk" patients: LDLC corticosteroids, however this regimen can begin with high-dose IVMP in cases of severe inflammation.	Discussed, but no recommendation.	
AU-TG (2017)[24]	No recommendation.	No recommendation.	
AHA (2017)[21]	For "high risk" patients: LDLC corticosteroids may be considered.	As an alternative to a second dose of IVIG, or following failure of a second dose of IVIG, high-dose IVMP with or without a weaning course of OPSL can be considered.	"High risk" not clearly defined.
ASP/ASC (2016)	No recommendation.	In cases of continuing treatment failure following a second course of IVIG, HDSC corticosteroids can be considered.	

Continued...

Table 2.7 continued...

Guideline	Primary Adjunctive Therapy	Treatment of IVIG Resistance	Comment
DM (2015)[33]	No recommendation.	In cases of continuing treatment failure following a second course of IVIG, high-dose IVMP followed by a weaning course of OPSL can be considered.	
UK (2002)[34]	No recommendation.	As an alternative to a second dose of IVIG, either HDSC or LDLC corticosteroids can be used.	

CRP, C-reactive protein; HDSC, high-dose, short course (corticosteroids); HLH, haemophagocytic lymphohistiocytosis; IFX, infliximab; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LDLC, low-dose, long course (corticosteroids); MAS, macrophage activation syndrome; OPSL, oral prednisolone.

Conclusions

While corticosteroids were once contraindicated in KD, it now seems that their use is generally safe and may indeed be beneficial in selected cases. There is some evidence that corticosteroids alone might be effective as primary therapy for KD, however few studies have been conducted.[9,295] Issues with availability and acceptability of IVIG mean that this possibility should be pursued.

Most trials, however, have focused on corticosteroids as primary adjunctive therapy. Meta-analyses have demonstrated improved coronary outcomes in favour of primary adjunctive corticosteroids, but also highlight significant heterogeneity in patient selection, treatment protocols, and outcome measures. These issues severely limit the ability to pool the results of studies, making research must less cost-effective.

It has been suggested that KD research should seek to emulate paediatric oncology research, in which almost all children are enrolled into research and international collaboration is the norm.[144,382] Without broad consensus around key points of KD trial design this will not be possible. Collaborative fora for KD research, established more than three decades ago,[130] should focus on harmonising key definitions to enhance future clinical research.

Part 5: Biologic Agents

Background

The term 'biologics', though imprecisely defined, is typically applied to a large and diverse group of therapeutic molecules that are designed to interact with biological processes in a highly specific manner, and which require advanced biological (rather than purely chemical) processes for their manufacture.[383,384] Almost all of the molecules included in this review all act by modulating ligand-receptor binding (by binding to the ligand or receptor), with some able to induce cell lysis in specific circumstances.

The aim of this review is to identify biologic agents relevant to KD and briefly summarise the rationale for their use and (where possible) evidence for their efficacy. While much of the literature on the inflammatory milieu of KD is inferred from a mouse model of coronary inflammation,[*] this review will aim to present what is known from studies of KD in humans.

TNF-α Blockade: Infliximab and Etanercept

Tumour necrosis factor-α (TNF-α) is a proinflammatory cytokine that plays a central role in the pathogenesis of a number of autoimmune and inflammatory conditions, including KD. TNF-α is produced by a range of cell types, notably macrophages and monocytes, in response to a range of stimuli[†]. It is expressed as a membrane-bound protein (which is biologically active with juxtacrine signalling activity[389]) and is cleaved by TNF-α-converting enzyme (TACE) to liberate the soluble form of TNF-α.[389] The effects of TNF-α in the target cells (involving the up-regulation of pro-inflammatory cytokines and chemokines via the up-regulation of the NF-κB transcription factor) is mediated by two TNF-α receptors: TNFR1 and TNFR2.[389,390] TNFR1 is constitutively expressed in all nucleated cells, while the expression of TNFR2 is inducible in certain cell types. Both TNFR1 and TNFR2 can be cleaved by matrix metalloproteinases to liberate a soluble fragment that can bind TNF-α, acting as a negative control mechanism.[389]

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[*] Certain strains of inbred mice develop coronary arteritis following the intraperitoneal injection of the purified cell-wall extract of group B *Lactobacillus casei* (LCWE).[385] This has been proposed as a model of KD, and has informed much of our understanding of the immunopathology of coronary arteritis.[386] Some findings regarding the proximate mechanisms of aneurysm formation appear to correlate well with findings from human KD research—notably the importance of matrix metalloproteinase 9 (MMP9) in the destruction of vascular collagen.[387] Yet LCWE-induced arteritis is not KD (LCWE having no proposed role in the aetiopathogenesis of the latter), and the validity of the model with regards to upstream mechanisms is far from clear.

[†] The canonical pathway—elucidated by researchers at the Sloan-Kettering Institute—involves TNF-α production by macrophages in response to bacterial lipopolysaccharide (endotoxin).[388]

It is well established that serum TNF-α is increased in KD,[391*] and while early work suggested that those with coronary aneurysms had higher levels of the cytokine subsequent research has yielded conflicting results.[395,396] A number of biologic agents have been produced that block the action of TNF-α[389†]; of these only infliximab and etanercept have been used in KD.[397]

Infliximab

Infliximab (*Remicade*®) is a mouse-human chimeric monoclonal antibody[‡] against TNF-α.[398] It binds TNF-α in its membrane bound, soluble, and receptor-bound forms, and is thought to act via the sequestration of circulating TNF-α and the removal of TNF-α expressing cells (via a range of cytotoxic pathways).[398] It was first approved by the US Food and Drug Administration (FDA) for the treatment of Crohn's disease in 1998, and for rheumatoid arthritis the following year.[399] It is now approved for use in a wide range of inflammatory conditions, including ulcerative colitis, plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis.

The first use of infliximab in KD was reported by Weiss *et al* in 2004.[400] They described a 3-year-old boy who, despite multiple infusions of IVIG and repeated treatment with pulse corticosteroids, had ongoing systemic inflammation and developed significant aneurysms of multiple coronary arteries. A single dose of infliximab (using a protocol recently approved for rheumatoid arthritis) resulted in prompt defervescence and normalisation of inflammatory markers. A retrospective review the following year identified 17 patients in whom infliximab had been used for refractory KD[401]; response to therapy was seen in 14[§] patients. Results of the first prospective trial[**] of infliximab in KD were published in 2008.[404] Twenty-four children with IVIG-resistant KD[††] and coronary artery dilatation were randomly allocated to receive either a second dose of IVIG or infliximab (5 mg/kg); those who failed

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[*] Although given the centrality of TNF-α to the inflammatory response, this is hardly surprising.[388,392–394]

[†] Currently approved agents for TNF-α blockade include etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab. Thalidomide and its derivatives also have anti-TNF-α effects.

[‡] Infliximab comprises mouse-derived anti-TNF-α variable regions fused to human IgG1 constant region.[398]

[§] Response could not be assessed in one patient who underwent plasmapheresis 12 hours after the infliximab infusion.

[**] The study was a multi-centre, randomised, open-label trial conducted at 6 centres in the United States. The primary outcomes were safety, tolerability, and pharmacokinetics of infliximab, rather than response to treatment or coronary outcomes. It was fundamental to the establishment of the Kawasaki Disease Comparative Effectiveness (KIDCARE) trial,[402,403] included in the meta-analysis discussed in the following paragraphs.

[††] IVIG resistance was defined as persistent or recrudescent fever between 48 hours and 7 days after the end of the first IVIG infusion.

to respond were re-allocated to the alternate therapy[*]. While the study was underpowered to evaluate non-inferiority[†], more children in the infliximab group (11/12) responded to therapy than did children in the IVIG group (8/12); coronary outcomes were similar between groups.

Subsequent trials have been assessed in a number of systematic reviews and meta-analyses,[405–410] of which the most recent was by Kabbaha *et al* in 2022.[405] Prospective trials of infliximab versus a second dose of IVIG for children with IVIG resistance were included, with four studies meeting the inclusion criteria—two from the USA, one from Japan, and one from South Korea.[54,403,404,411‡] No study reported a statistically significant difference between groups in terms of coronary outcomes, and the pooled risk ratio (RR 1.20; 95% CI 0.54, 2.63[§]) also indicated no difference between groups.[**] Rates of secondary treatment failure were significantly lower among those given infliximab versus IVIG (RR 0.40; 95% CI 0.25, 0.64), and there was a trend in favour of infliximab in terms of adverse events (RR 0.63; 95% CI 0.18, 1.12). A more inclusive meta-analysis that included nine trials generated similar results.[406] At least two further prospective trials are currently underway.[††]

A number of studies have considered infliximab for primary adjunctive therapy in KD.[312,403,412] Tremoulet *et al* randomised 196 children with acute KD to receive infliximab or placebo prior to primary therapy with IVIG, with the primary outcome being rate of IVIG resistance.[412] There was no difference between groups in the rates of IVIG resistance, length of hospital admission, or coronary outcomes; those who received infliximab had fewer IVIG-relative infusion reactions shorter duration of fever. Dionne *et al* randomised 121 children with acute KD and coronary abnormalities[‡‡] at diagnosis to receive IVIG with adjunctive corticosteroids, IVIG with infliximab, or IVIG alone.[312] Adjunctive therapy with either infliximab or corticosteroids was associated with lower rates of aneurysm progression[§§] compared with IVIG alone.

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[*] I.e., those with ongoing inflammation after treatment in the infliximab group were given an additional dose of IVIG; those in the IVIG group were given infliximab.
[†] The sample size was calculated based on the primary outcomes (safety, tolerability, and pharmacokinetics of infliximab).
[‡] The South Korean study[411] was considered to have a high risk of bias, and in sensitivity analysis was excluded from analysis.
[§] Risk ratio of less than 1 favours infliximab.
[**] On subgroup analysis there was a trend in favour of IVIG (RR 1.92, 95% CI 0.70 to 5.27), whereas there was a trend in favour of infliximab in the Japanese and Korean studies (RR 0.48, 95% CI 0.11 to 2.06).
[††] NCT02298062 and ChiCTR1900027954.
[‡‡] Defined as a z-score of ≥2.5 to <10 in the right main coronary artery or left anterior descending artery.
[§§] This was statistically significant, but only for the proportion of children who had an increase in the size of their most dilated vessel by at least 1 z-score.

Etanercept

Etanercept (*Enbrel*®) is a fusion protein that combines the extracellular domain of the soluble receptor TNFR2 with an IgG1 Fc region.[398] The main mechanism of etanercept is to bind soluble (rather than membrane- or receptor-bound) TNF-α, and it does not result in meaningful cell lysis. It is used for similar dermatologic and musculoskeletal indications as infliximab, but is ineffective in inflammatory bowel disease.[398] Direct comparative trials comparing infliximab with etanercept for most conditions are mission, and comparisons are further compounded as infliximab is almost always combined with methotrexate for the treatment of rheumatoid arthritis, whereas etanercept can be used as monotherapy.[413] While infliximab is administered intravenously,[414] etanercept is given subcutaneously.[415]

The safety of etanercept as adjunctive therapy in KD was demonstrated by Choueiter *et al* in a small, prospective, open-label trial that was designed to assess safety and pharmacokinetics.[416] This lead to the establishment of the Etanercept as Adjunctive Treatment for Acute Kawasaki Disease (EATAK) trial, which published its results in 2019.[417] Children with acute KD (205 in total) were randomised to receive etanercept (0.8 mg/kg by subcutaneous injection) or placebo immediately after primary therapy with IVIG, then weekly for two further doses. The primary outcome was IVIG resistance, with coronary artery z-scores assessed as secondary outcomes. The study reported lower rates of IVIG resistance in the etanercept group, however lower than expected rates of resistance overall resulted in the study being underpowered to demonstrate a difference.[418] There were no meaningful differences in coronary outcomes between groups.

Safety of TNF-α Blockade

Much of the safety data for infliximab and etanercept comes from studies in patients on long-term therapy for chronic inflammatory conditions.[419] Opportunistic infections are a known risk of TNF-α blockade; early trials of infliximab in rheumatoid arthritis observed higher rates of serious infections* in the infliximab groups (at all doses) than a methotrexate alone group.[420] Indeed, infliximab appears to carry a higher risk for opportunistic infections than does etanercept.[421†] The relevance of this risk for children with KD (who would typically receive only a single dose of infliximab) is unclear—while few trials reported time-to-infection outcomes, there is evidence that infection risk is associated with cumulative drug exposure.[423] Indeed, in their meta-analysis Kabbaha *et al* found no evidence of higher rates of infection among

* Pneumonia was the main serious infection, with four patients having reactivation of laten tuberculosis.

† Although the risk of infection is unclear: patients treated with infliximab for inflammatory bowel disease did not have significantly higher rates of opportunistic infections.[422]

those treated with infliximab versus a second course of IVIG (however the included trials only involved 199 patients).[405] Postmarketing surveillance in Japan identified six cases of infections among 291 children treated for KD with infliximab, of which only three were classified as serious (identified as influenza, bronchitis, and orbital cellulitis).[424]

There are reports of an increased risk of cancer with TNF-α blockade, however the risk in the paediatric population—and especially to children with KD—is unclear. In a meta-analysis of randomised controlled trials in adults, Askling *et al* identified 130 cases of cancer among 15,418 patients treated with TNF-α inhibitors (0.84%) compared with 48 cases among 7,486 controls (0.64%)[425]; they concluded that the risk of cancer associated with TNF-α blockade remained uncertain. Given the background risk of cancer in adults compared with children, and the relative contribution of acquired versus inborne genetic risk factors, it is reasonable to expect that the absolute risk of cancer among children receiving TNF-α inhibitors should be very low.[426] The matter is however complicated by the increased risk of cancer conferred by the conditions for which TNF-α inhibitors are most commonly prescribed to children (juvenile idiopathic arthritis and inflammatory bowel disease).[426] Taking that into consideration, there is currently little evidence to suggest that children are exposed to additional risk by TNF-α blockade.[427,428]

IL-1 Blockade: Anakinra and Canakinumab

The interleukin 1 (IL-1) family* is an evolutionarily ancient group of cytokines that play key roles in orchestrating the early innate immune response to pathogen-associated molecules and tissue damage.[429,430] IL-1 comprises two cytokines—IL-1α and IL-1β; though these cytokines act on the same receptor† and have identical effects they differ in tissue distribution, post-transcriptional control, and means of expression.[429,430] IL-1α is expressed by diverse cell types (particularly epithelial cells) and is predominantly membrane-bound with juxtacrine functions. IL-1β is predominantly expressed by monocytes and macrophages, and is secreted as a soluble molecule capable of systemic effects.[429] The production of IL-1 is tightly controlled via numerous negative feedback loops; these include the IL-1R antagonist IL-1Ra‡ and the complex control of post-transcriptional processing of pro-IL-1β by caspase-1§.[431] IL-1β

* Members of the family include IL-1α, IL-1β, IL-1Ra, IL-18, and IL-33, among many others.[429]

† A heterodimer comprised of IL-1 receptor 1 (IL-1R1) and IL-1 receptor associated protein (IL-1RAP).

‡ The expression of IL-1Ra is upregulated in response to the same stimuli that stimulate IL-1β.[429] IL-1Ra binds tightly to the IL-1R without inducing inflammatory effects.

§ IL-1β is transcribed as an inactive precursor (pro-IL-1β), which must be activated by the enzyme caspase-1. Caspase-1, in turn, is tightly controlled by a complex system of intracellular proteins called the inflammasome(s).[431,432] Inherited perturbations of this control mechanism which are responsible for a group of

production by monocytes and macrophages is stimulated by molecular signals* associated with pathogens (notably bacterial lipopolysaccharide), as well as endogenous signals of tissue damage (such as adenosine triphosphate and uric acid crystals).[429] IL-1 exerts potent pro-inflammatory effects on diverse cell types. Of relevance to KD, IL-1 directs neutrophilic response to tissue damage, with enhanced release of immature cells from the marrow and local recruitment and tissue invasion via cytokine and chemokine release and upregulated expression of adhesins.[432,433] IL-1 also supports T cell response by promoting the proliferation and survival of both effector and helper T cells, while blunting the control of regulatory T cells.[429,434–436]

Early attempts to apply IL-1 blockade to KD were informed by observations from animal models and clinical research. Peripheral blood mononuclear cells from children with acute KD secrete high levels of IL-1 (particularly so from those with coronary aneurysms).[437–439] Further, IL-1β was found to be necessary for the development of coronary arteritis in LCWE-treated mice.[440] Clinicians were also encouraged by the safety profile of IL-1 blockers (particularly anakinra).[441]

Anakinra

Anakinra (*Kineret*®), a recombinant form of IL-1Ra, was introduced in 1993 and originally used for the treatment of rheumatoid arthritis.[442] It has since been approved for a wide range of autoimmune and autoinflammatory conditions, including systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease; cryopyrin associated periodic syndrome (CAPS), familial Mediterranean fever (FMF), Muckle-Wells syndrome (MWS), TNF-receptor-associated periodic syndrome (TRAPS), and other autoinflammatory syndromes—including gout.[442]

The first reported use of anakinra in KD was published by Shafferman *et al* in 2014.[443] They described the case of an 11-week-old girl with apparent KD complicated by macrophage activation syndrome (MAS)† who responded to the use of anakinra. A subsequent literature review identified 11 case reports of the use of anakinra in KD.[446] In all cases the use of anakinra was followed

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inherited autoinflammatory conditions including Muckle-Wells syndrome, familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disease (NOMID), and Familial Mediterranean Fever (FMF).

* Via highly conserved sensing mechanisms such as Toll-like receptors.[429]

† Macrophage activation syndrome (MAS) refers to secondary haemophagocytic lymphohistiocytosis occurring in the context of rheumatological conditions—most prominently systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease, but also systemic lupus erythematosus and KD, among others.[444] It is characterised by overactivation of T lymphocytes (particularly $CD8^+$T cells) and macrophages, with consequent systemic hyperinflammation; the condition carries a high mortality.[444,445] The role of IL-1β in MAS has been hypothesised, in part, due to its importance in SJIA.[444]

by defervescence and striking reductions in CRP, and in most cases by a reduction in coronary artery z-scores.

Two phase II clinical trials of anakinra in KD have been published as of early 2023.[55,447] The KAWAKINRA trial was a multi-centre, single-arm open-label, phase IIa dose escalation trial of anakinra in children with IVIG-resistant KD.[55] Enrolled patients received escalating daily doses of subcutaneous anakinra; if defervescence occurred then that dose was continued to two weeks. The study was small (16 patients included in the intention-to-treat group) and had a high rate of post-enrolment exclusion and protocol deviation, with only 8 patients completing the study per-protocol. Administration of anakinra was followed by resolution of fever in most of the patients in both the intention-to-treat group (12/16, 75%) and the per-protocol group (7/8, 87.5%). Safety and tolerability were excellent, with only one adverse event (swelling and pruritis at the injection site) attributed to the anakinra.

The ANAKID trial was a multi-centre*, single-arm open-label, phase I/IIa dose escalation trial of anakinra as primary adjunctive therapy for children with KD and coronary artery abnormalities† at diagnosis.[447] All participants received subcutaneous anakinra‡ for 2 weeks, with those found to have persistent coronary dilatation§ at that timepoint continuing on the study drug for an additional 4 weeks. Importantly, most of the participants had also received adjunctive infliximab prior to enrolment.** Anakinra was deemed to be safe and tolerable, with no serious adverse events attributable to the study drug.

Neither of these trials were designed to assess efficacy, however both provided further evidence in support of anakinra's safety in this patient population and contributed important pharmacokinetic data†† for future Phase III trials.

Canakinumab

Canakinumab (*Ilaris*®)is a human IgG monoclonal antibody against IL-1β. It has similar indications to anakinra, but has the theoretical benefit of being specific for IL-1β; it also has a much longer half-life requiring dosing only

* There were two recruitment sites (Rady Children's Hospital San Diego and Boston Children's Hospital), with 20/22 patients recruited at the former.
† Coronary abnormalities were defined as a z-score ≥2.5 in the left anterior descending coronary artery of right main coronary artery.
‡ The first two doses were given IV as park of the pharmacokinetics study.
§ Z-score ≥2.0 in the left anterior descending coronary artery of right main coronary artery.
** The use of infliximab (5 mg/kg) prior to the IVIG infusion is standard of care at Randy Children's Hospital San Diego—all 20 patients recruited at that site received infliximab.
†† The pharmacokinetic findings of these studies are outside the scope of this review.

every 2–3 months.[448] It has been intensively studied for a possible role in the secondary prevention of myocardial infarction, with the CANTOS trial demonstrating a small but significant reduction in adverse coronary outcomes among those with a prior myocardial infarction and evidence residual low-level inflammation.[449] While no reports of the use of canakinumab in KD have been published, a phase II trial of its use as both primary adjunctive therapy and secondary therapy is currently underway.[450]

Other Novel Agents

Tocilizumab

There has been recent interest in the use of tocilizumab for the treatment of systemic inflammatory conditions associated with severe COVID-19.[451,452] Tocilizumab (*Actemra*®) is a human monoclonal IgG antibody against the receptor for IL-6.[453] IL-6 is a pleiotropic proinflammatory cytokine capable of inducing diverse inflammatory changes in multiple organ systems.[454*] IL-6 is thought to play an important role in a number of autoimmune conditions, however its role in some systemic hyperinflammatory states† has suggested its possible usefulness in KD.

Tocilizumab was investigated as a potential agent for use in IVIG-resistant KD in a small pilot study in Japan.[455] The study was stopped after recruitment of only four patients due to safety concerns. While all four patients had rapid defervescence and improvements in inflammatory markers shortly after receiving tocilizumab, two patients (neither of whom had coronary abnormalities at the time of receiving tocilizumab) had progressive development of giant coronary aneurysms. No further studies have assessed tocilizumab in KD, and its use in multisystem inflammatory syndrome in children (MIS-C, a COVID-19-associated hyperinflammatory syndrome) is controversial.[456]

Abciximab

Abciximab (*ReoPro*®) is a monoclonal antibody fragment against the platelet glycoprotein IIb/IIIa receptor used to prevent acute thrombotic complications in acute coronary syndrome (and especially during percutaneous coronary intervention).[457] The glycoprotein IIb/IIIa receptor is extremely abundant on the surface of platelets (~80,000 copies per platelet).[458] The receptor binds

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* These include: Upregulated hepatic synthesis of proinflammatory proteins (mostly α- and β-globulins, including CRP, antitrypsin, serum amyloid protein A, and hepcidin; also fibrinogen and complement C3); increased vascular permeability; promotion of a hypercoagulable state through various mechanisms, including increased expression of tissue factor; and impaired cardiomyocyte contractility.

† The most striking of these is cytokine release syndrome (CRS), a severe systemic hyperinflammatory state associated with novel T-cell engaged therapies used for some haematological malignancies. Tocilizumab has shown highly promising results in small case series of CRS.[454]

fibrinogen and von Willebrand factor with low affinity, however platelet activation causes a conformational change resulting in high-affinity binding that results in platelet aggregation and the formation of a stable platelet plug.[458]

Etheridge *et al* reported a case of rapid regression of large coronary aneurysms in a 4-month-old girl with KD who received abciximab following percutaneous angiography for thromboprophylaxis.[459] They hypothesized that abciximab might promote vascular remodelling in patients with coronary aneurysms. Two small retrospective cohort studies have provided evidence in support of this hypothesis.[460,461] In both studies children with significant coronary aneurysms who received abciximab had greater reduction in coronary artery z-scores at follow-up than children who did not receive abciximab. Due to their small numbers and retrospective nature both are at risk for selection bias. There is a need for prospective controlled trials to validate these findings.

Conclusions

There is significant interest in advancing the therapeutic armamentarium available for the treatment of KD—both in response to the high cost of IVIG and the significant proportion of children for whom it is ineffective. Biologic agents may offer a solution. While the development of these synthetic molecules incurs high up-front costs, scalable manufacturing processes mean that the marginal cost of production diminishes with expanded production.[462] Further, the rapid development of biosimilar molecules* can enable market competition to influence price before the reference molecule comes off patent.[463]

While some novel therapies have demonstrated promising results, the case of tocilizumab is a cautionary one. Despite over fifty years of research, the immunopathophysiology of KD is poorly understood.[464–467] The anti-inflammatory agents described in this review act on major cytokines central to the inflammatory process to produce non-specific immunosuppression. Greater understanding of the mechanisms of immune dysfunction and aneurysm formation seen in KD might inform more targeted therapies. An exemplar biopharmaceutical in this regard is vedolizumab.

Vedolizumab (*Entyvio*®) is a humanised monoclonal antibody against the $\alpha_4\beta_7$ integrin used for the treatment of inflammatory bowel disease.[468] Integrins are heterodimeric cell surface receptors that mediate cell-to-cell adhesion. Integrins composed of different α and β subunit combinations have varied expression in different cell types with diverse functions. Integrin $\alpha_4\beta_7$ is

* "Biosimilars" replicate the in vivo activity of a reference biologic agent to which they are similar but not identical. By contrast, generic drugs are exact copies of a reference drug that can be marketed once the original patent has expired. Biosimilars that replicate both infliximab and etanercept are currently available.[463]

expressed on the surface of leukocytes and binds with high specificity with its ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1).[*] MAdCAM-1, in turn, is expressed by intestinal endothelial cells. This receptor-ligand binding event facilitates the rolling adhesion and firm adhesion necessary for tissue-specific leukocyte migration.[469] Vedolizumab prevents leukocyte migration into the intestinal mucosa, thereby selectively suppressing inflammation in the gastrointestinal tract.[†] It has proven to be both safe and effective in the management of inflammatory bowel disease.[470–472]

Gene expression profiling has been used to identify potential target molecules for future therapeutic agents in KD. Hoang *et al* compared gene expression patterns between children with acute KD, children with known bacterial and viral infections, and well controls.[464] Their findings provided further evidence of the centrality of IL-1β to KD, and acknowledged the roles of other pathways (including integrins and matrix metalloproteinases) in diverse infectious conditions.

Such approaches are exciting, however key underlying principles are worthy of note. The categories on which machine learning algorithms process bioinformatics data are provided *a priori*. As such, the validity of the results is dependent on the ontological and methodological precision with which the categories are defined and implemented. This highlights again the need for a collaborative effort to produce carefully designed criteria and definitions for KD research.

[*] Integrin $\alpha_4\beta_7$ also binds to vascular cell adhesion molecule-1 (VCAM-1) and fibronectin.

[†] This specificity is of critical importance to vedolizumab's safety. Natalizumab, a monoclonal antibody against the α_4 subunit, lacks this specificity. It is used in the treatment of multiple sclerosis but is associated with the development of progressive multifocal leukoencephalopathy due to reactivation of latent JC virus.[468] Vedolizumab's specificity for intestinal mucosa obviates this risk. Vedolizumab was specifically designed not only with receptor specificity, but also ligand specificity. The binding of integrin $\alpha_4\beta_7$ to VCAM-1 and fibronectin is not inhibited by vedolizumab. One final innovation is critical to vedolizumab's safety: the Fc region of the antibody was mutated to reduce its ability to facilitate both complement-dependent and cellular-dependent cytotoxicity.[468]

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Chapter 3

The following manuscript, entitled "Variation in the management of Kawasaki disease in Australia and New Zealand: A survey of paediatricians" was published in *The Journal of Paediatrics and Child Health* in 2020. The study, which analysed responses by Australian and New Zealand clinicians to an international survey, sought to describe local practice regarding the diagnosis and management of KD. The findings indicated that there was consensus around the use of IVIG but revealed significant disagreements with regard to the use of aspirin in the acute phase of KD, as well as around criteria for the diagnosis of IVIG-resistant disease.

Practitioner's descriptions of their own practice (reported below) can be compared with observed practice, which is presented in Chapter 6.

I am grateful to Dr Audrey Dionne, and her collaborators in the USA and Canada, for providing access to the Australian and New Zealand responses to their survey. A global analysis of the survey was published in *The Archives of Disease in Childhood* in 2019[*].

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ORIGINAL ARTICLE

Variation in the management of Kawasaki disease in Australia and New Zealand: A survey of paediatricians

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Aim: This study aimed to describe the current management practices for Kawasaki disease (KD) in Australia and New Zealand.

Methods: We performed a secondary analysis on the Australian and New Zealand responses to a large international survey of clinicians' perspectives on KD diagnosis and management.

Results: There was general consensus among Australian and New Zealand clinicians regarding the indications for intravenous immunoglobulin and aspirin in the management of acute KD. There was less consensus on the dose of these agents, the definition and management of treatment-resistant KD and the approach to long-term thromboprophylaxis.

Conclusion: Most clinicians use intravenous immunoglobulin for primary treatment of KD. There is variation regarding other aspects of KD diagnosis and important management issues. Future studies should confirm whether this reported variation occurs in real-world practice and assess potential impacts on patient outcome.

Key words: aspirin; intravenous immunoglobulin; Kawasaki disease; mucocutaneous lymph node syndrome.

What is already known on this topic

1 Kawasaki disease (KD) is an inflammatory condition of childhood that has become a leading cause of paediatric acquired heart disease in the developed world.
2 Intravenous immunoglobulin (IVIG) improves coronary artery outcomes in KD.
3 Guidelines for the management of KD vary around the world.

What this paper adds

1 Clinicians almost unanimously reported prescribing IVIG for the primary therapy of acute KD, albeit at varying dose.
2 There is disagreement about the dose of aspirin in acute KD.
3 There is a lack of consensus around important definitions, such as for IVIG-resistant disease.

Kawasaki disease (KD) is a systemic vasculitis that predominantly affects young children. The coronary arteries are particularly affected, and KD can result in morbidity ranging from mild and self-resolving coronary dilatation to permanent and life-threatening aneurysms.[1] Intravenous immunoglobulin (IVIG) reduces the incidence of coronary artery lesions from 25 to 5%[2,3] and it is the only intervention supported by evidence from randomised controlled trials. Aspirin has historically had two roles in KD: reducing inflammation and preventing thrombosis; evidence supporting either in KD is weak.[4,5] Additional therapies (such as corticosteroids and biologics) are also used, although with less certainty as to their efficacy and role.[6–8]

KD that does not respond to primary therapy with IVIG ('IVIG resistance') is an important clinical entity, with non-responders at higher risk for coronary complications.[9] Despite this, there is no consensus definition of IVIG resistance, and little evidence to inform management. Other areas of uncertainty include risk stratification of patients, adjunctive primary therapy and the need for and duration of thromboprophylaxis.[10]

A recently published international survey of physicians' approach to KD diagnosis and management identified significant practice variation, particularly around adjunctive primary therapy and the definition and management of IVIG-resistant disease.[11] We undertook a secondary analysis of the Australian and New Zealand responses in

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this study to assess local areas of practice variation and to inform future local guidelines.

Methods

We analysed responses from paediatricians in Australia and New Zealand participating in an international survey of clinicians' perspectives on KD diagnosis and management.[11] The survey was hosted on SurveyMonkey and was distributed through professional and personal networks world-wide. As the survey was not sent to a pre-determined number of clinicians, it was not possible to assess the response rate. Responses were recorded between January and August 2017. This subgroup analysis was planned in advance of results from the international survey having been analysed.

There were 42 questions in total (see Supporting Information); respondents could choose not to answer questions. All responses were anonymous and providing demographic data was optional. Respondents reported their clinical speciality and were categorised as either generalists (general paediatricians and those who reported no speciality) or specialists (paediatric sub-specialities: cardiology, infectious disease, immunology or rheumatology).

Statistical analyses (frequencies and proportions) were performed using Stata/IC 15.1 for Mac (StataCorp 2017. Stata Statistical Software: Release 15; StataCorp, College Station, TX, USA). Data are presented as proportions (percent), with non-responses subtracted from the denominator.

The international survey received ethical approval from the Centre Hospitalier Universitaire Sainte-Justine in Montreal, Canada. This sub-analysis was granted exemption from ethical approval by the Sydney Children's Hospitals Network.

Results

Respondents

There were 108 respondents from Australia and New Zealand; descriptive statistics of respondents are provided in Table 1. Sixty-nine percent (74 of 108) of respondents were general paediatricians and 81% (88 of 108) reported managing fewer than five cases of KD per year.

Diagnosis

Respondents were asked how evidence for alternative or concurrent diagnoses would affect their certainty of the diagnosis of KD (in a child fulfilling the full clinical criteria as defined by the American Heart Association (AHA)[10]). Clinicians retained the diagnosis of KD in the following clinical scenarios: lobar pneumonia on chest radiograph, 85% (92 of 108); influenza on nasal swab polymerase chain reaction, 76% (82 of 108); and toxic shock syndrome by clinical criteria, 51% (55 of 108) (Table S1, Supporting Information).

Fifty-one percent (40 of 78) of general paediatricians reported that echocardiography was readily available at the time of diagnosis compared to 93% (28 of 30) of paediatric subspecialists (Table S2, Supporting Information). When asked about the definition of giant coronary aneurysms 37% (40 of 108) of respondents reported using absolute measurement of the internal diameter (≥8 mm) and 44% (48 of 108) reported using normalised values (*Z*-score) (Table S3, Supporting Information).

Primary therapy

Almost all respondents stated that they use IVIG as primary therapy for children with KD (96–97%, depending on coronary artery status at diagnosis) (Fig. 1, Tables S4–S8, Supporting Information). The majority of respondents used a dose of 2 g/kg; however, almost 10% used a dose of 1 g/kg (Fig. 1, Table S5, Supporting Information).

Aspirin was widely prescribed at the time of diagnosis; only 11% of respondents (11 of 104) indicated that they would not prescribe aspirin for children with normal coronary arteries at diagnosis. Respondents in New Zealand showed a general consensus in favour of moderate-dose aspirin (30–50 mg/kg/day), regardless of the coronary artery status. There was less consensus among respondents in Australia: 48% (38 of 80) used low-dose aspirin (3–5 mg/kg/day) from diagnosis for children with normal coronary arteries, while 25% each (20 of 80) used moderate-dose and high-dose (80–100 mg/kg/day) aspirin in these patients. Australian respondents were more likely to use high-dose aspirin as the coronary artery involvement worsened, with 40% (27 of 67) prescribing high-dose aspirin for children with giant aneurysms (Fig. 2, Tables S9–S11, Supporting Information).

Use of corticosteroids as adjunctive primary therapy varied by coronary artery status at diagnosis. Four percent (4 of 104) of respondents selected corticosteroids for children with normal coronary arteries at diagnosis, compared with 12% (12 of 98) and 21% (19 of 89) for children with non-giant and giant aneurysms, respectively. Specialists were more likely than generalists to use corticosteroids. Biologic agents were infrequently used as primary adjunctive therapy (Fig. 1, Tables S4–S8, Supporting Information).

IVIG resistance: Definition and management

Respondents were asked how many hours after the end of IVIG infusion they would consider persistent or recrudescent fever to signify IVIG non-response. Fever at 24 h was most commonly selected by respondents in Australia (59% of Australians selected 24 h vs. 27% of New Zealanders), whereas fever at 48 h was most commonly selected by respondents in New Zealand (50% of New Zealanders vs. 20% of Australians) (Fig. 3, Table S12, Supporting Information).

Retreatment with IVIG was the most commonly selected therapy for the management of IVIG-resistant KD (89–92% of respondents, depending on coronary artery status at diagnosis). Corticosteroids were the second most commonly selected therapy for IVIG-resistant KD (51–54% of respondents). Corticosteroids were commonly co-administered with the second dose of IVIG (about 90% of those who selected corticosteroids also selected IVIG). Intravenous corticosteroids were favoured over oral corticosteroids. Infliximab (a tumour necrosis factor-alpha inhibitor) was the most commonly selected biologic agent and was used more commonly by specialists than generalists. Thirteen percent of respondents selected infliximab for a child with resistant KD and giant coronary aneurysms (Fig. 1, Tables S13–S15, Supporting Information).

Table 1 Descriptive statistics of survey respondents in Australia and New Zealand

	Australia No. (%)	New Zealand No. (%)	Total No. (%)
Gender			
Female	45 (55)	14 (54)	59 (55)
Male	36 (44)	12 (46)	48 (44)
Unknown	1 (1)	0 (0)	1 (1)
Total	82 (100)	26 (100)	108 (100)
Speciality			
General paediatrics	56 (68)	18 (69)	74 (69)
Cardiology	4 (5)	4 (15)	8 (7)
Infectious diseases	9 (11)	2 (8)	11 (10)
Immunology/rheumatology	9 (11)	2 (8)	11 (10)
None	4 (5)	0 (0)	4 (4)
Total	82 (100)	26 (100)	108 (100)
Years of practice			
≤5	20 (24)	3 (12)	23 (21)
6–1	18 (22)	7 (27)	25 (23)
11–15 years	10 (12)	3 (12)	13 (12)
16–20	15 (18)	6 (23)	21 (19)
>20	19 (23)	7 (27)	26 (24)
Total	82 (100)	26 (100)	108 (100)
KD patients in the last year			
<5	64 (78)	24 (92)	88 (81)
≥5	18 (22)	2 (8)	20 (19)
Total	82 (100)	26 (100)	108 (100)

KD, Kawasaki disease.

Thromboprophylaxis

Low-dose aspirin was the most commonly selected agent for long-term thromboprophylaxis. The proportion of respondents who used aspirin varied with the severity of coronary artery involvement at diagnosis: 18% of respondents (18 of 102) indicated that they would use long-term, low-dose aspirin for a child with normal coronary arteries at diagnosis, while 85% (76 of 89) would do so if there was persistent coronary artery dilatation. With increasing severity of coronary artery involvement, respondents were more likely to use alternative thromboprophylactic agents instead of, or in addition to, aspirin. For children with giant aneurysms, 57% (49 of 86) indicated that they would use another thromboprophylactic agent in the long term, either alone or in combination with aspirin. Of these, 61% (30 of 49) chose warfarin while 27% (13 of 49) and 22% (11 of 49), respectively, chose a dual anti-platelet agent or low-molecular weight heparin.

Discussion

We describe the management of KD across Australia and New Zealand, performing a subgroup analysis of the survey originally reported by Dionne *et al.*[11] That study described significant variation in the management of KD internationally; IVIG was widely accepted as first-line therapy, however, there was variation around dose. Other areas of variation included the definition and management of IVIG-resistant KD. We found consensus around the indications for IVIG but some variation around the dose used. The efficacy of IVIG in KD correlates with peak plasma immunoglobulin concentration,[12] and evidence from randomised controlled trials recommends the higher dose of 2 g/kg.[13] Current guidelines recommend a single dose of IVIG at 2 g/kg per dose, given as a single infusion (Table 2).[10,14,15]

We also found significant variation around aspirin dosage in acute KD. Aspirin has dual proposed roles in KD management: inhibition of platelet activation at lower doses (3–5 mg/kg/day) and anti-inflammatory effects at higher doses (>30 mg/kg/day).[16] There are no convincing data to suggest efficacy of higher dose aspirin compared with anti-platelet dose aspirin in preventing coronary aneurysms.[5,16] There is currently significant disagreement among international guidelines around the approach to aspirin during the acute phase of KD (Table 2). The AHA guidelines suggest it is reasonable to use aspirin at either 30–50 or 80–100 mg/kg/day until defervescence.[10] The guidelines from Starship Hospital (Auckland, New Zealand) recommend aspirin at 30–50 mg/kg/day, dropping to the lower anti-platelet dose after 1 week.[15] Clinical Practice Guidelines from the Royal Children's Hospital (Melbourne), widely used in Australia, recommend aspirin at 3–5 mg/kg/day from diagnosis; this is based on the lack of evidence for the efficacy of higher dose aspirin on coronary artery outcomes and considerable experience of low-dose aspirin for thromboprophylaxis.[14] This seems to be an area of marked deviation from international standard practice: the international survey that produced these data showed that of the

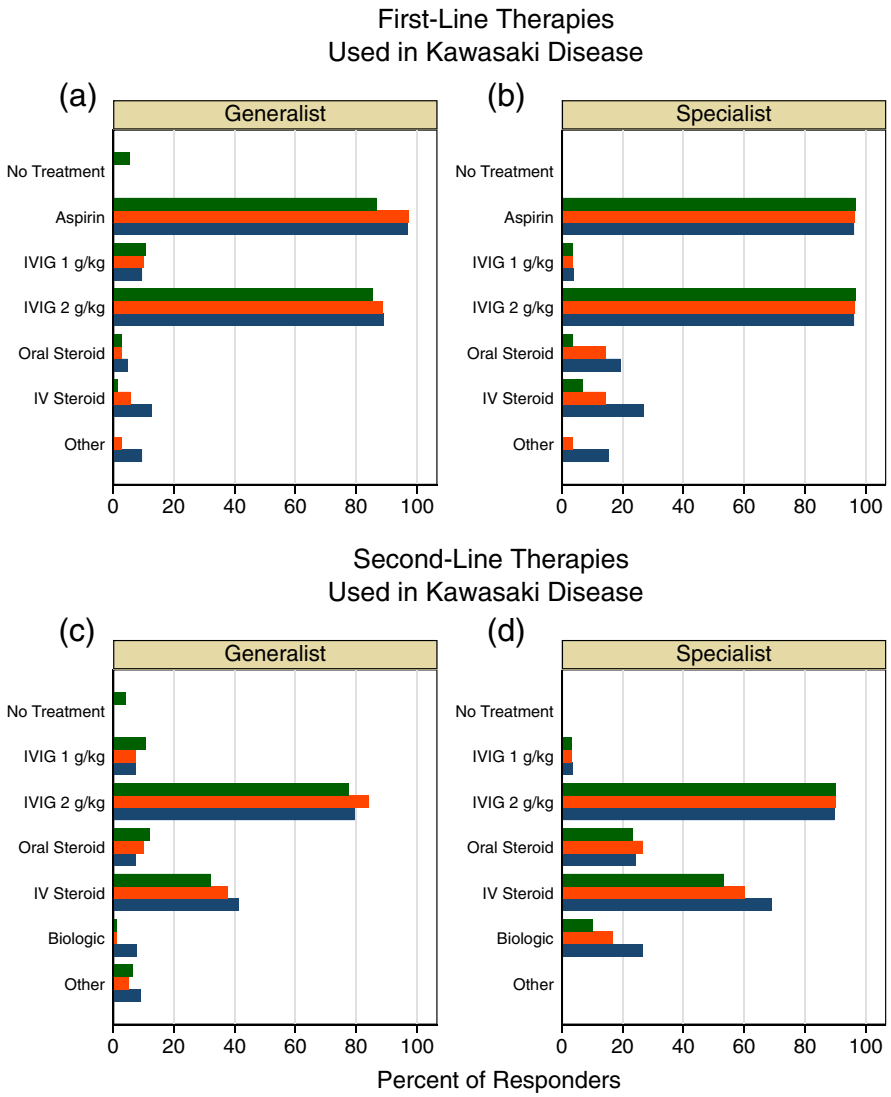

Fig. 1 Reported therapies used in the treatment of Kawasaki disease (KD) in Australia and New Zealand, by specialisation. Therapies selected by general paediatricians (a) and paediatric sub-specialists (b) for the first-line management of acute KD. The category 'Other' includes anti-tumour necrosis factor-alpha agents. Therapies selected by general paediatricians (c) and paediatric sub-specialist (d) for the treatment of intravenous immunoglobulin-resistant KD. The category 'Biologic' includes infliximab, etanercept, anakinra and canakinumab; the category 'Other' includes cyclosporine. Results are provided in detail in Supporting Information (■, normal coronaries; ■, non-giant aneurysms; ■, giant aneurysms).

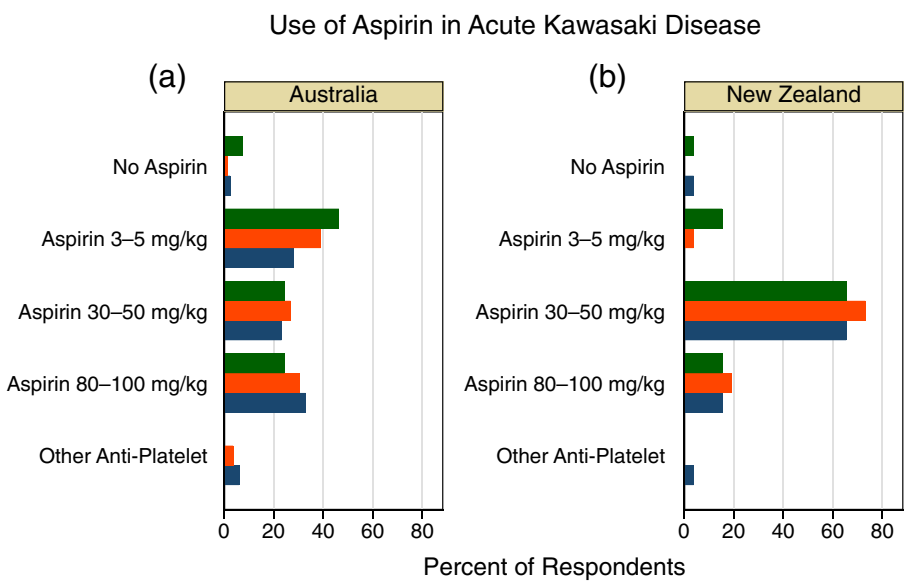

Fig. 2 Aspirin dose used in the febrile phase of Kawasaki disease (KD) in Australia and New Zealand, by country. Dose of aspirin selected by respondents in Australia (a) and New Zealand (b) for the treatment of KD during the febrile phase. Results are provided in detail in Supporting Information (■, normal coronaries; ■, non-giant aneurysms; ■, giant aneurysms).

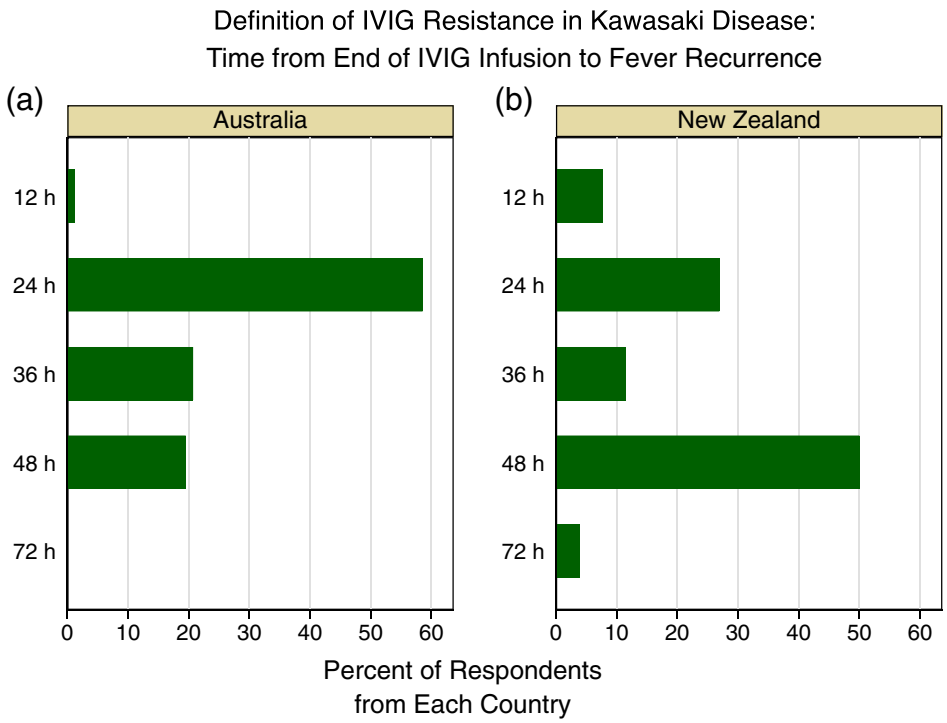

Fig. 3 Time after the first dose of intravenous immunoglobulin (IVIG) at which IVIG-resistant Kawasaki disease (KD) is diagnosed by the presence of fever in Australia and New Zealand, by country. IVIG-resistant KD is defined as persistence or recrudescence of fever after the first dose of IVIG; the time at which this diagnosis is made varies. Hours at which the presence of fever indicates failure to respond to treatment, as reported by respondents in Australia (a) and New Zealand (b). Results are provided in detail in Supporting Information.

Table 2 Summary of recommendations from the international Kawasaki disease management guidelines

Region	IVIG (g/kg)	Aspirin (mg/kg/day)	Definition of resistance (hours from treatment)	Treatment of IVIG resistance
Australia[14,25,26]	2	3–5	36	1 IVIG 2 Corticosteroids
Europe[27]	2	30–50 initially, then 3–5	36 or 48	1 IVIG 2 Corticosteroids 3 Biologics
Japan[28]	2	30–50 initially, then 3–5	24	1 IVIG 2 Corticosteroids 3 Biologics
New Zealand[15]	2	30–50 initially, then 3–5	48–72	1 IVIG 2 Corticosteroids 3 Biologics
North America[10]	2	30–50 or 80–100 initially, then 3–5	24 or 36	1 IVIG 2 Biologics 3 Corticosteroids
UK[29]	2	30–50 or 80–100 initially, then 3–5	36–48	1 IVIG 2 Corticosteroids 3 Biologics

Drawn from publicly available clinical practice guidelines. IVIG, intravenous immunoglobulin.

724 respondents only 13% used low-dose aspirin in acute KD.[17] In this context, it is not surprising to find lack of consensus in clinical practice.[5]

There was also considerable variation in practice with respect to management of IVIG resistance, which is inconsistently defined in the KD literature and in international guidelines (Table 2). Most definitions are based on the presence of ongoing inflammation after the first dose of IVIG – usually identified by the persistence or recrudescence of fever.[10,14,15,18,19] Studies on the use of adjunctive anti-inflammatory agents have shown that earlier defervescence does not necessarily reduce the risk of coronary artery dilatation.[4,6,20] Conversely, concurrent infection is a common finding in

acute KD, complicating the interpretation of ongoing fever.[21] A fever-based definition of resistant disease may lack sensitivity and specificity. The treatment of resistant KD is an active area of clinical research, and there is a need to establish consensus on the definition to facilitate comparison across studies.[22]

There is variation in the management of treatment-resistant KD.[10] After a second dose of IVIG, corticosteroids were the most common adjunctive therapy. This is in keeping with the AHA guidelines, although evidence is limited for this approach.[10,23] Infliximab was the most commonly used biologic agent for resistant KD. Infliximab has been studied as therapy for IVIG-resistant KD and reductions in inflammatory cytokines and duration of fever have been shown; however, there is no evidence that this approach alters coronary outcomes.[18] Given the relatively low incidence of significant coronary artery damage in KD, and the heterogeneity of treatment approaches in this patient group, these studies are likely underpowered to demonstrate a lack of benefit; further collaborative studies into the utility of infliximab in the treatment of KD are required.[24]

In keeping with the findings of the international survey, we found variation in the approach to ongoing thromboprophylaxis among respondents; however, our findings must be interpreted with caution. Ongoing anticoagulation is complex and highly individualised, based on both current coronary size and worst-ever coronary size.[10] These decisions are typically made by cardiologists, who were relatively under-represented in this survey.

We acknowledge some key limitations of this study. First, only a small number of paediatricians in Australia and New Zealand participated in the survey; the distribution of the survey was not systematic and may over-represent practice in tertiary institutions and major cities. Second, the questions were by necessity theoretical and assumed that coronary artery status was known at the time of diagnosis. This information is frequently unavailable when initial management decisions are made; however, assessing all possible scenarios of clinical uncertainty would have lengthened the survey to make the participant burden unacceptable. Third, respondents were asked about scenarios that may fall outside their scope of practice (e.g. general paediatricians managing thromboprophylaxis in children with giant coronary artery aneurysms) and were not given the option to indicate uncertainty; responses may not have reflected management decisions that are often taken after specialist multidisciplinary discussions. We are currently undertaking prospective studies on KD in Australia to better describe these and other aspects of KD management.

Conclusion

We demonstrated consensus in clinical practice around the indications for IVIG and aspirin in the management of KD in Australia and New Zealand. There was a lack of consensus on the dose of each agent and in the definition of and approach to the management of IVIG-resistant KD. These findings should inform the development and dissemination of local practice guidelines. They also reinforce the ongoing need for international collaboration in KD research to develop and follow common definitions (such as the definition of IVIG resistance) and to clarify the roles of adjunctive therapies.

Acknowledgement

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Diagnosis of Kawasaki disease in the context of alternate diagnoses.
Table S2. Availability of echocardiography in Australia by specialty.
Table S3. Criteria used to define giant coronary aneurysms.
Table S4. Intravenous immunoglobulin as the primary treatment.
Table S5. Primary therapy for Kawasaki disease.
Table S6. Primary therapy for Kawasaki disease in children with normal coronary arteries at diagnosis.
Table S7. Primary therapy for Kawasaki disease in children with non-giant coronary aneurysms at diagnosis.
Table S8. Primary therapy for Kawasaki disease in children with giant coronary aneurysms at diagnosis.
Table S9. Aspirin during acute Kawasaki disease: normal coronary arteries at diagnosis.
Table S10. Aspirin during acute Kawasaki disease: non-giant aneurysms at diagnosis.
Table S11. Aspirin during acute Kawasaki disease: giant aneurysms at diagnosis.
Table S12. Definition of resistance by time to defervescence.
Table S13. Secondary therapy for Kawasaki disease in children with normal coronary arteries at diagnosis.
Table S14. Secondary therapy for Kawasaki disease in children with non-giant aneurysms at diagnosis.
Table S15. Secondary therapy for Kawasaki disease in children with giant aneurysms at diagnosis.

Variation in the Management of Kawasaki Disease in Australia and New Zealand: A survey of paediatricians.

Supplementary Results

Table 3.S1: Diagnosis of KD in the Context of Alternate Diagnoses

	Generalist or Specialist					
	Generalist		Specialist		Total	
	No.	%	No.	%	No.	%
KD & Pneumonia (KD should NOT be excluded):						
Strongly Disagree	0	0	0	0	0	0
Disagree	3	4	3	10	6	6
Neither	8	10	2	7	10	9
Agree	43	55	16	53	59	55
Strongly Agree	24	31	9	30	33	31
Total	78	100	30	100	108	100
KD & Influenza (KD should NOT be excluded):						
Strongly Disagree	1	1	1	3	2	2
Disagree	9	12	4	13	13	12
Neither	9	12	2	7	11	10
Agree	34	44	14	47	48	44
Strongly Agree	25	32	9	30	34	31
Total	78	100	30	100	108	100
KD & Toxic Shock Syndrome (KD should NOT be excluded):						
Strongly Disagree	2	3	1	3	3	3
Disagree	17	22	7	23	24	22
Neither	21	27	5	17	26	24
Agree	21	27	9	30	30	28
Strongly Agree	17	22	8	27	25	23
Total	78	100	30	100	108	100

Question (Pneumonia): *If a child with the clinical features of Kawasaki disease also has lobar pneumonia diagnosed radiologically at the same time, this should not exclude the diagnosis of Kawasaki disease.*

Question (Influenza): *If a child with the clinical features of Kawasaki disease also has a influenza infection diagnosed by nasal swab PCR at the same time, this should not exclude the diagnosis of Kawasaki disease.*

Question (Toxic Shock Syndrome): *If a child with the clinical features of Kawasaki disease also fulfils the diagnostic criteria for toxic shock syndrome at the same time, this should not exclude the diagnosis of Kawasaki disease.*

Table 3.S2: Availability of Echocardiography in Australia by Specialty

	Generalist or Specialist					
	Generalist		Specialist		Total	
	No.	%	No.	%	No.	%
Availability of echocardiograms:						
Readily available	40	51	28	93	68	63
Most of the time not available	22	28	2	7	24	22
No access, transfer needed	16	21	0	0	16	15
Total	78	100	30	100	108	100

Question: *Is echocardiogram readily available in your practice, or does its availability limit patients' evaluation and follow-up?*

Table 3.S3: Criteria Used to Define Giant Coronary Aneurysms

	Definition of Giant Coronary Artery Aneurysm							
	≥8mm / Z-score		≥8mm		Z-score		Total	
	No.	%	No.	%	No.	%	No.	%
Generalist or Specialist:								
Generalist	18	23	25	32	35	45	78	100
Specialist	2	7	15	50	13	43	30	100
Total	20	19	40	37	48	44	108	100

Question: *In patients with coronary artery complications following Kawasaki disease, how would you define giant aneurysms? Please select one response.*

Survey respondents could chose the following answers: Coronary artery internal luminal diameter ≥8mm and/or Z-score cut-off, Coronary artery internal luminal diameter ≥8 mm in all patients, and Coronary artery Z-score cut-off in all patients. For brevity these have been replaced with: ≥8mm / Z-score, ≥8mm, and Z-score, respectively.

Table 3.S4: IVIG as Primary Treatment

	Generalist or Specialist					
	Generalist		Specialist		Total	
	No.	%	No.	%	No.	%
All children with KD should have IVIG as initial therapy:						
Strongly Disagree	5	6	1	3	6	6
Disagree	1	1	0	0	1	1
Neither	2	3	0	0	2	2
Agree	23	29	4	13	27	25
Strongly Agree	47	60	25	83	72	67
Total	78	100	30	100	108	100

Question: *To what extent do you agree or disagree with the following statement on the treatment of Kawasaki disease: All children with KD should have IVIG as initial therapy.*

Table 3.S5: Primary Therapy for Kawasaki Disease

	Coronary Status		
	Normal Coronaries	non-Giant Aneurysms	Giant Aneurysms
	%	%	%
Treatment:			
No Treatment	4	0	0
Aspirin	89	97	97
IVIG 1 g/kg	9	8	8
IVIG 2 g/kg	88	91	91
Oral Steroid	3	6	9
IV Steroid	3	8	17
Anti-TNF-α	0	1	7
Other	0	2	4

Question: *In your current practice, which therapies are part of your initial treatment of patients diagnosed with acute Kawasaki disease?*

Table 3.S6: Primary Therapy for Kawasaki Disease in Children with Normal Coronary Arteries at Diagnosis

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
None:												
No	68	96	7	100	11	100	11	100	3	75	100	96
Yes	3	4	0	0	0	0	0	0	1	25	4	4
Total	71	100	7	100	11	100	11	100	4	100	104	100
Aspirin:												
No	8	11	0	0	0	0	1	9	2	50	11	11
Yes	63	89	7	100	11	100	10	91	2	50	93	89
Total	71	100	7	100	11	100	11	100	4	100	104	100
IVIG 1 g/kg:												
No	64	90	6	86	11	100	11	100	3	75	95	91
Yes	7	10	1	14	0	0	0	0	1	25	9	9
Total	71	100	7	100	11	100	11	100	4	100	104	100
IVIG 2 g/kg:												
No	9	13	1	14	0	0	0	0	2	50	12	12
Yes	62	87	6	86	11	100	11	100	2	50	92	88
Total	71	100	7	100	11	100	11	100	4	100	104	100
Oral Steroid:												
No	69	97	6	86	11	100	11	100	4	100	101	97
Yes	2	3	1	14	0	0	0	0	0	0	3	3
Total	71	100	7	100	11	100	11	100	4	100	104	100
IV Steroid:												
No	70	99	6	86	10	91	11	100	4	100	101	97
Yes	1	1	1	14	1	9	0	0	0	0	3	3
Total	71	100	7	100	11	100	11	100	4	100	104	100
Anti-TNF-α:												
No	71	100	7	100	11	100	11	100	4	100	104	100
Total	71	100	7	100	11	100	11	100	4	100	104	100

Continued...

. . . Table 3.S6 Continued

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Other:												
No	71	100	7	100	11	100	11	100	4	100	104	100
Total	71	100	7	100	11	100	11	100	4	100	104	100

Question: *In your current practice, which therapies are part of your initial treatment of patients diagnosed with acute Kawasaki disease? Please select all treatments that you use some or most of the time for each category ['category' refers to coronary artery status at diagnosis]. You can select more than one answer.*

Table 3.S7: Primary Therapy for Kawasaki Disease in Children with non-Giant Coronary Aneurysms at Diagnosis

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
None:												
No	66	100	8	100	10	100	10	100	4	100	98	100
Total	66	100	8	100	10	100	10	100	4	100	98	100
Aspirin:												
No	2	3	0	0	0	0	1	10	0	0	3	3
Yes	64	97	8	100	10	100	9	90	4	100	95	97
Total	66	100	8	100	10	100	10	100	4	100	98	100
IVIG 1 g/kg:												
No	59	89	7	88	10	100	10	100	4	100	90	92
Yes	7	11	1	12	0	0	0	0	0	0	8	8
Total	66	100	8	100	10	100	10	100	4	100	98	100
IVIG 2 g/kg:												
No	7	11	1	12	0	0	0	0	1	25	9	9
Yes	59	89	7	88	10	100	10	100	3	75	89	91
Total	66	100	8	100	10	100	10	100	4	100	98	100
Oral Steroid:												
No	64	97	6	75	10	100	8	80	4	100	92	94
Yes	2	3	2	25	0	0	2	20	0	0	6	6
Total	66	100	8	100	10	100	10	100	4	100	98	100
IV Steroid:												
No	62	94	7	88	9	90	8	80	4	100	90	92
Yes	4	6	1	12	1	10	2	20	0	0	8	8
Total	66	100	8	100	10	100	10	100	4	100	98	100
Anti-TNF-α:												
No	66	100	8	100	9	90	10	100	4	100	97	99
Yes	0	0	0	0	1	10	0	0	0	0	1	1
Total	66	100	8	100	10	100	10	100	4	100	98	100

Continued...

. . . Table 3.S7 Continued

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Other:												
No	65	98	8	100	10	100	10	100	3	75	96	98
Yes	1	2	0	0	0	0	0	0	1	25	2	2
Total	66	100	8	100	10	100	10	100	4	100	98	100

Question: *In your current practice, which therapies are part of your initial treatment of patients diagnosed with acute Kawasaki disease? Please select all treatments that you use some or most of the time for each category ['category' refers to coronary artery status at diagnosis]. You can select more than one answer.*

Table 3.S8: Primary Therapy for Kawasaki Disease in Children with Giant Coronary Aneurysms at Diagnosis

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
None:												
No	59	100	7	100	9	100	10	100	4	100	89	100
Total	59	100	7	100	9	100	10	100	4	100	89	100
Aspirin:												
No	2	3	0	0	0	0	1	10	0	0	3	3
Yes	57	97	7	100	9	100	9	90	4	100	86	97
Total	59	100	7	100	9	100	10	100	4	100	89	100
IVIG 1 g/kg:												
No	53	90	6	86	9	100	10	100	4	100	82	92
Yes	6	10	1	14	0	0	0	0	0	0	7	8
Total	59	100	7	100	9	100	10	100	4	100	89	100
IVIG 2 g/kg:												
No	6	10	1	14	0	0	0	0	1	25	8	9
Yes	53	90	6	86	9	100	10	100	3	75	81	91
Total	59	100	7	100	9	100	10	100	4	100	89	100
Oral Steroid:												
No	56	95	5	71	8	89	8	80	4	100	81	91
Yes	3	5	2	29	1	11	2	20	0	0	8	9
Total	59	100	7	100	9	100	10	100	4	100	89	100
IV Steroid:												
No	51	86	5	71	7	78	7	70	4	100	74	83
Yes	8	14	2	29	2	22	3	30	0	0	15	17
Total	59	100	7	100	9	100	10	100	4	100	89	100
Anti-TNF-α:												
No	56	95	7	100	8	89	8	80	4	100	83	93
Yes	3	5	0	0	1	11	2	20	0	0	6	7
Total	59	100	7	100	9	100	10	100	4	100	89	100

Continued...

. . . Table 3.S8 Continued

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Other:												
No	57	97	6	86	9	100	10	100	3	75	85	96
Yes	2	3	1	14	0	0	0	0	1	25	4	4
Total	59	100	7	100	9	100	10	100	4	100	89	100

Question: *In your current practice, which therapies are part of your initial treatment of patients diagnosed with acute Kawasaki disease? Please select all treatments that you use some or most of the time for each category ['category' refers to coronary artery status at diagnosis]. You can select more than one answer.*

Table 3.S9: Aspirin During Acute Kawasaki Disease: Normal Coronary Arteries at Diagnosis

	Responder's country					
	Australia		New Zealand		Total	
	No.	%	No.	%	No.	%
No Aspirin:						
No	74	92	24	96	98	93
Yes	6	8	1	4	7	7
Total	80	100	25	100	105	100
Low-Dose Aspirin:						
No	42	52	21	84	63	60
Yes	38	48	4	16	42	40
Total	80	100	25	100	105	100
Medium Dose Aspirin:						
No	60	75	8	32	68	65
Yes	20	25	17	68	37	35
Total	80	100	25	100	105	100
High Dose Aspirin:						
No	60	75	21	84	81	77
Yes	20	25	4	16	24	23
Total	80	100	25	100	105	100
Other Antiplatelet:						
No	80	100	25	100	105	100
Total	80	100	25	100	105	100

Question: *In your current practice, which aspirin dosing do you use in the treatment of patients with Kawasaki disease at time of initial diagnosis?*

Table 3.S10: Aspirin During Acute Kawasaki Disease: non-Giant Aneurysms at Diagnosis

	Responder's country					
	Australia		New Zealand		Total	
	No.	%	No.	%	No.	%
No Aspirin:						
No	76	99	25	100	101	99
Yes	1	1	0	0	1	1
Total	77	100	25	100	102	100
Low-Dose Aspirin:						
No	45	58	24	96	69	68
Yes	32	42	1	4	33	32
Total	77	100	25	100	102	100
Medium Dose Aspirin:						
No	55	71	6	24	61	60
Yes	22	29	19	76	41	40
Total	77	100	25	100	102	100
High Dose Aspirin:						
No	52	68	20	80	72	71
Yes	25	32	5	20	30	29
Total	77	100	25	100	102	100
Other Antiplatelet:						
No	74	96	25	100	99	97
Yes	3	4	0	0	3	3
Total	77	100	25	100	102	100

Question: *In your current practice, which aspirin dosing do you use in the treatment of patients with Kawasaki disease at time of initial diagnosis?*

Table 3.S11: Aspirin During Acute Kawasaki Disease: Giant Aneurysms at Diagnosis

	Responder's country					
	Australia		New Zealand		Total	
	No.	%	No.	%	No.	%
No Aspirin:						
No	65	97	21	95	86	97
Yes	2	3	1	5	3	3
Total	67	100	22	100	89	100
Low-Dose Aspirin:						
No	44	66	22	100	66	74
Yes	23	34	0	0	23	26
Total	67	100	22	100	89	100
Medium Dose Aspirin:						
No	48	72	5	23	53	60
Yes	19	28	17	77	36	40
Total	67	100	22	100	89	100
High Dose Aspirin:						
No	40	60	18	82	58	65
Yes	27	40	4	18	31	35
Total	67	100	22	100	89	100
Other Antiplatelet:						
No	62	93	21	95	83	93
Yes	5	7	1	5	6	7
Total	67	100	22	100	89	100

Question: *In your current practice, which aspirin dosing do you use in the treatment of patients with Kawasaki disease at time of initial diagnosis?*

Table 3.S12: Definition of Resistance by Time to Defervescence

	Time for definition of resistant KD (hrs)									
	12 hrs		24 hrs		36 hrs		48 hrs		72 hrs	
	No.	%	No.	%	No.	%	No.	%	No.	%
Responder's country:										
Australia	1	1	48	59	17	21	16	20	0	0
New Zealand	2	8	7	27	3	12	13	50	1	4
Total	3	3	55	51	20	19	29	27	1	1
Responder's Specialty Group:										
General Paediatrics	3	4	33	45	14	19	23	31	1	1
Cardiology	0	0	5	62	2	25	1	12	0	0
Infectious Disease	0	0	7	64	1	9	3	27	0	0
Immunology/Rheumatology	0	0	7	64	2	18	2	18	0	0
None	0	0	3	75	1	25	0	0	0	0
Total	3	3	55	51	20	19	29	27	1	1

Question: *A patient is treated for Kawasaki disease with IVIG and has persistent fever. How many hours after the end of IVIG infusion would you consider persistent or recrudescent fever to signify IVIG non-response?*

Table 3.S13: Secondary Therapy for Kawasaki Disease in Children with Normal Coronary Arteries at Diagnosis

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
None:												
No	69	97	8	100	11	100	11	100	3	75	102	97
Yes	2	3	0	0	0	0	0	0	1	25	3	3
Total	71	100	8	100	11	100	11	100	4	100	105	100
IVIG 1 g/kg:												
No	64	90	7	88	11	100	11	100	3	75	96	91
Yes	7	10	1	12	0	0	0	0	1	25	9	9
Total	71	100	8	100	11	100	11	100	4	100	105	100
IVIG 2 g/kg:												
No	15	21	1	12	1	9	1	9	2	50	20	19
Yes	56	79	7	88	10	91	10	91	2	50	85	81
Total	71	100	8	100	11	100	11	100	4	100	105	100
Oral Steroid:												
No	62	87	6	75	8	73	9	82	4	100	89	85
Yes	9	13	2	25	3	27	2	18	0	0	16	15
Total	71	100	8	100	11	100	11	100	4	100	105	100
IV Steroid:												
No	47	66	5	62	4	36	5	45	4	100	65	62
Yes	24	34	3	38	7	64	6	55	0	0	40	38
Total	71	100	8	100	11	100	11	100	4	100	105	100

Continued...

. . . Table 3.S13 Continued

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Infliximab:												
No	70	99	8	100	9	82	10	91	4	100	101	96
Yes	1	1	0	0	2	18	1	9	0	0	4	4
Total	71	100	8	100	11	100	11	100	4	100	105	100
Etanercept:												
No	71	100	8	100	10	91	11	100	4	100	104	99
Yes	0	0	0	0	1	9	0	0	0	0	1	1
Total	71	100	8	100	11	100	11	100	4	100	105	100
Anakinra:												
No	71	100	8	100	10	91	11	100	4	100	104	99
Yes	0	0	0	0	1	9	0	0	0	0	1	1
Total	71	100	8	100	11	100	11	100	4	100	105	100
Canakinumab:												
No	71	100	8	100	11	100	11	100	4	100	105	100
Total	71	100	8	100	11	100	11	100	4	100	105	100
Cyclosporine:												
No	71	100	8	100	11	100	11	100	4	100	105	100
Total	71	100	8	100	11	100	11	100	4	100	105	100
Other:												
No	67	94	8	100	11	100	11	100	3	75	100	95
Yes	4	6	0	0	0	0	0	0	1	25	5	5
Total	71	100	8	100	11	100	11	100	4	100	105	100

Question: *In your current practice, which therapies are part of your treatment of patients with acute Kawasaki disease who have not responded to initial treatment (i.e. have ongoing or recrudescence of their fever despite initial therapy)? Please select all treatment that you use some or most of the time for each category ['category' refers to coronary artery status at diagnosis]. You can select more than one answer.*

Table 3.S14: Secondary Therapy for Kawasaki Disease in Children with non-Giant Aneurysms at Diagnosis

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
None:												
No	65	100	8	100	11	100	11	100	4	100	99	100
Total	65	100	8	100	11	100	11	100	4	100	99	100
IVIG 1 g/kg:												
No	61	94	7	88	11	100	11	100	3	75	93	94
Yes	4	6	1	12	0	0	0	0	1	25	6	6
Total	65	100	8	100	11	100	11	100	4	100	99	100
IVIG 2 g/kg:												
No	10	15	1	12	1	9	1	9	1	25	14	14
Yes	55	85	7	88	10	91	10	91	3	75	85	86
Total	65	100	8	100	11	100	11	100	4	100	99	100
Oral Steroid:												
No	58	89	6	75	8	73	8	73	4	100	84	85
Yes	7	11	2	25	3	27	3	27	0	0	15	15
Total	65	100	8	100	11	100	11	100	4	100	99	100
IV Steroid:												
No	39	60	4	50	4	36	4	36	4	100	55	56
Yes	26	40	4	50	7	64	7	64	0	0	44	44
Total	65	100	8	100	11	100	11	100	4	100	99	100
Infliximab:												
No	64	98	8	100	9	82	8	73	4	100	93	94
Yes	1	2	0	0	2	18	3	27	0	0	6	6
Total	65	100	8	100	11	100	11	100	4	100	99	100
Etanercept:												
No	65	100	8	100	10	91	10	91	4	100	97	98
Yes	0	0	0	0	1	9	1	9	0	0	2	2
Total	65	100	8	100	11	100	11	100	4	100	99	100

Continued...

. . . Table 3.S14 Continued

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Anakinra:												
No	65	100	8	100	10	91	11	100	4	100	98	99
Yes	0	0	0	0	1	9	0	0	0	0	1	1
Total	65	100	8	100	11	100	11	100	4	100	99	100
Canakinumab:												
No	65	100	8	100	11	100	11	100	4	100	99	100
Total	65	100	8	100	11	100	11	100	4	100	99	100
Cyclosporine:												
No	65	100	8	100	11	100	11	100	4	100	99	100
Total	65	100	8	100	11	100	11	100	4	100	99	100
Other:												
No	62	95	8	100	11	100	11	100	3	75	95	96
Yes	3	5	0	0	0	0	0	0	1	25	4	4
Total	65	100	8	100	11	100	11	100	4	100	99	100

Question: *In your current practice, which therapies are part of your treatment of patients with acute Kawasaki disease who have not responded to initial treatment (i.e. have ongoing or recrudescence of their fever despite initial therapy)? Please select all treatment that you use some or most of the time for each category ['category' refers to coronary artery status at diagnosis]. You can select more than one answer.*

Table 3.S15: Secondary Therapy for Kawasaki Disease in Children with Giant Aneurysms at Diagnosis

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
None:												
No	64	100	8	100	10	100	11	100	4	100	97	100
Total	64	100	8	100	10	100	11	100	4	100	97	100
IVIG 1 g/kg:												
No	60	94	7	88	10	100	11	100	3	75	91	94
Yes	4	6	1	12	0	0	0	0	1	25	6	6
Total	64	100	8	100	10	100	11	100	4	100	97	100
IVIG 2 g/kg:												
No	13	20	1	12	1	10	1	9	1	25	17	18
Yes	51	80	7	88	9	90	10	91	3	75	80	82
Total	64	100	8	100	10	100	11	100	4	100	97	100
Oral Steroid:												
No	59	92	7	88	7	70	8	73	4	100	85	88
Yes	5	8	1	12	3	30	3	27	0	0	12	12
Total	64	100	8	100	10	100	11	100	4	100	97	100
IV Steroid												
No	36	56	3	38	3	30	3	27	4	100	49	51
Yes	28	44	5	62	7	70	8	73	0	0	48	49
Total	64	100	8	100	10	100	11	100	4	100	97	100
Infliximab:												
No	59	92	8	100	6	60	7	64	4	100	84	87
Yes	5	8	0	0	4	40	4	36	0	0	13	13
Total	64	100	8	100	10	100	11	100	4	100	97	100
Etanercept:												
No	63	98	8	100	9	90	10	91	4	100	94	97
Yes	1	2	0	0	1	10	1	9	0	0	3	3
Total	64	100	8	100	10	100	11	100	4	100	97	100

Continued...

. . . Table 3.S15 Continued

	Responder's Specialty Group											
	General Paediatrics		Cardiology		Infectious Disease		Immunology/Rheum.		None		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Anakinra:												
No	62	97	8	100	9	90	11	100	4	100	94	97
Yes	2	3	0	0	1	10	0	0	0	0	3	3
Total	64	100	8	100	10	100	11	100	4	100	97	100
Canakinumab:												
No	64	100	8	100	10	100	11	100	4	100	97	100
Total	64	100	8	100	10	100	11	100	4	100	97	100
Cyclosporine:												
No	62	97	8	100	10	100	11	100	4	100	95	98
Yes	2	3	0	0	0	0	0	0	0	0	2	2
Total	64	100	8	100	10	100	11	100	4	100	97	100
Other:												
No	60	94	8	100	10	100	11	100	3	75	92	95
Yes	4	6	0	0	0	0	0	0	1	25	5	5
Total	64	100	8	100	10	100	11	100	4	100	97	100

Question: *In your current practice, which therapies are part of your treatment of patients with acute Kawasaki disease who have not responded to initial treatment (i.e. have ongoing or recrudescence of their fever despite initial therapy)? Please select all treatment that you use some or most of the time for each category ['category' refers to coronary artery status at diagnosis]. You can select more than one answer.*

Chapter 4

The following manuscript, entitled "Epidemiology of Kawasaki disease in Australia using two nationally complete datasets" was published in *The Journal of Paediatrics and Child Health* in 2021. The study sought to update the KD incidence estimate for Australia by analysing two independent nation-wide datasets: one that recorded hospitalisations (using ICD discharge diagnosis codes), and another that recorded the allocation of IVIG by The Australian Red Cross Blood Service (Now Australian Red Cross Lifeblood).

We reported that the incidence of KD had been rising, on average, 3.5% annually over a 25-year period. We also observed some evidence of seasonal variation in the rates of IVIG use for KD, noting that this pattern appeared to vary by latitude.

This research was made possible by the provision of data by Australian Red Cross Lifeblood. Australian governments fund Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian community. I acknowledge the support of the data custodians in facilitating access to these data. I am grateful to Dr Saundankar (Great Ormond Street Children's Hospital, Formerly of Children's Cardiac Centre, Princess Margaret Hospital for Children, Perth, Western Australia, Australia), who provided access to data from her study into the epidemiology of KD in Western Australia. This study was supported by a National Blood Sector Research and Development Pilot Project grant (ID111) from the National Blood Authority of Australia.

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ORIGINAL ARTICLE

Epidemiology of Kawasaki disease in Australia using two nationally complete datasets

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Aim: The incidence of Kawasaki disease (KD) is reported to be increasing in some populations. We sought to describe long-term trends in the incidence and epidemiology of KD in Australia over 25 years.

Methods: Two nationally complete administrative datasets relevant to KD in Australia were analysed and compared. The Australian Red Cross Lifeblood *Supply Tracking Analysis Reporting System* (STARS) recorded all doses of immunoglobulin (IVIG) approved in Australia between January 2007 and June 2016. The Australian Institute of Health and Welfare *National Hospital Morbidity Database* (NHMD) records all episodes of care in hospitals across Australia. Data relevant to KD were extracted an analysed, with comparisons made for the period of data overlap.

Results: During the period of data overlap (2007–2015) the IVIG treatment rate in the 0- to 4-year age group (calculated from STARS) was 14.31 per 100 000 person-years (95% confidence interval 13.67–14.97). The hospitalisation rate in the same age group (calculated from the NHMD) was 14.99 per 100 000 person-years (95% confidence interval 14.33–15.66). Hospitalisation rates rose at an average rate of 3.54% annually over the 25 years to 2017 in the 0- to 4-year age group, almost exclusively in the 1- to 4-year age group.

Conclusions: There is evidence of increasing KD diagnosis in Australia. Similar trends have also been reported in Asia but not in North America or Europe. Increasing diagnosis may reflect a true increase in disease incidence, increasing recognition or overdiagnosis. Further research is needed to determine the cause for these trends.

Key words: epidemiology; intravenous immunoglobulin; Kawasaki disease; rheumatology; routinely collected health data; vasculitis.

What is already known on this topic

1 The most recent estimate of KD incidence in Australia was 9.34 per 100,000 children under the age of 5 per year.
2 There have been inconsistent reports of increasing incidence of KD from around the world.
3 There has been little research on the epidemiology of KD in Australia.

What this paper adds

1 We report the current national KD incidence based on two distinct complete national datasets of admissions and treatment.
2 We report a clear increasing trend to KD hospitalisation over the last 25 years.
3 We report evidence of seasonal variation in the rates of IVIG treatment for KD.

Kawasaki disease (KD) is a systemic vasculitis that predominantly affects children under 5 years of age[1] and is a leading cause of acquired heart disease among children.[2] Intravenous immunoglobulin (IVIG) at a dose of 2 g/kg significantly reduces the incidence of coronary artery aneurysms[3] and is recommended as first-line treatment for KD.[1] Reported incidence of KD varies, with Japan reporting rates as high as 330.2 per 100 000 person-years in the 0- to 4-year age group[4]; rates outside of East Asia are at least an order of magnitude lower.[5,6] Many countries in Asia have reported increasing incidence, although this has been reported less consistently in Europe and North America.[7,8]

Two studies have investigated the incidence of KD in Australia. Royle *et al.* conducted a nation-wide survey of paediatricians between 1993 and 1995, reporting an incidence of 3.7 per

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100 000 person-years in the 0- to 4-year age group.[9] Saundankar *et al* undertook a retrospective discharge audit and case review in Western Australia between 1979 and 2009, reporting an increase in incidence from 2.82 to 9.34 per 100 000 person-years in the 0- to 4-year age group over that period.[10]

Studies of KD incidence often use the hospitalisation rate as a surrogate for the incidence rate; however, factors such as multiple admissions in the same illness episode is likely to overestimate the true incidence.[11] We sought to address these methodological shortcomings by using multiple overlapping sources. We analysed datasets of IVIG-treatment and hospitalisations that overlapped for 9 years, determining the IVIG-treatment rate and the hospitalisation rate for that period. We further described trends in KD hospitalisation over a 25-year period and undertook a spatiotemporal analysis of IVIG treatment data to assess for seasonal trends in KD treatment rates.

Methods

Two datasets were used to calculate rates of KD diagnosis, each of which was nationally complete over a given period. The Supply Tracking And Reporting System (STARS) recorded doses of IVIG supplied by the national blood bank, while the National Hospital Morbidity Database (NHMD) recorded hospitalisations at all Australian hospitals. The study was conducted in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data statement.[12]

Supply tracking and reporting system

Australian Red Cross Lifeblood (previously the Australian Red Cross Blood Service) is the single provider of publicly funded blood products in Australia. Strict criteria govern the access to publicly funded IVIG, with KD an approved indication since 1993.[13] STARS was the inventory management system used by Australian Red Cross Lifeblood for immunoglobulin products from 2006 to 2016. We analysed records of all doses of IVIG supplied for KD from January 2007 to June 2016; data available included patient name, date of birth, sex and weight; IVIG dose and brand; and the request date and prescribing hospital. We were able to account for children who received multiple doses of IVIG to determine the total number of IVIG-treated KD episodes (Supplementary Methods in Appendix S1).

National Hospital Morbidity Database

The Australian Institute of Health and Welfare is Australia's national agency for information and statistics on Australia's health and welfare; it publishes data on all episodes of care ('separations') at all Australian hospitals since 1993, available to the public online as the NHMD.[14] We retrieved all separations for which the primary diagnosis was KD (using International Classification of Disease (ICD) discharge codes ICD-9-CM 446.1 for 1993–1998 and ICD-10-AM M30.3 thereafter) between July 1993 and June 2018. The number of separations was presented in aggregated form but could be disaggregated by age bracket and sex for Australian financial years (1 July to 30 June). From these data, we derived the total number of hospitalisations for KD (Supplementary Methods in Appendix S1).

Data linkage between the datasets was not possible due to the aggregated nature of the NHMD. Age-specific IVIG-treatment rates and hospitalisation rates were calculated from STARS and the NHMD, respectively, using census data from the *Australian Bureau of Statistics*.[15] Both were annualised by Australian financial years, and summarised by five 5-year periods: 1993–1997, 1998–2002, 2003–2007, 2008–2012 and 2013–2017.

To assess the accuracy of the IVIG-treatment rate, we compared IVIG-treated episodes of KD with data on the incidence of KD in Western Australia published by Saundankar *et al.* during the 3 years that the data overlapped (2007–2009).[10] We then compared the IVIG-treatment and the hospitalisation rate for the 9 years that the STARS dataset and the NHMD overlapped. Finally, we extended the analysis of each dataset depending on their scope and spaciotemporal resolution: the NHMD was analysed for its full 25 years to examine trends in KD hospitalisation over time and spatiotemporal analysis of the STARS dataset assessed for seasonal patterns in KD treatment rates.

Table 1 Kawasaki disease (KD) cases identified by Saundankar *et al.* and Supply Tracking Analysis Reporting System (Australian Red Cross Lifeblood) (STARS) during overlapping years, 2007–2009

	Saundankar *et al.* ($n = 41$)	STARS ($n = 45$)
Cases, *n* (%)		
0–4 years	29 (71)	34 (76)
5–9 years	7 (17)	8 (18)
Rate per 100 000 person-years (95% CI)		
0–4 years	6.77 (4.54–9.73)	7.94 (5.50–11.10)
5–9 years	1.68 (0.68–3.47)	1.92 (0.83–3.79)

Cases in Saundankar *et al.* were derived from a state-wide retrospective discharge audit and chart review in Western Australia. Cases in STARS represent intravenous immunoglobulin-treated episodes of KD in Western Australia. CI, confidence interval.

Table 2 Kawasaki disease (KD) cases identified in Supply Tracking Analysis Reporting System (Australian Red Cross Lifeblood) (STARS) and the National Hospital Morbidity Database (Australian Institute of Health and Welfare) (NHMD) during overlapping years, 2007–2015

	STARS ($n = 2590$)	NHMD ($n = 2682$)
Cases, *n* (%)		
0–4 years	1885 (73.0)	1974 (73.6)
5–9 years	579 (22.4)	606 (22.6)
Rate per 100 000 person-years (95% CI)		
0–4 years	14.31 (13.67–14.97)	14.99 (14.33–15.66)
5–9 years	4.57 (4.21–4.96)	4.78 (4.41–5.18)

Cases in STARS represent intravenous immunoglobulin-treated episodes of KD. Cases in the NHMD represent hospitalizations for which the primary discharge diagnosis was KD. CI, confidence interval.

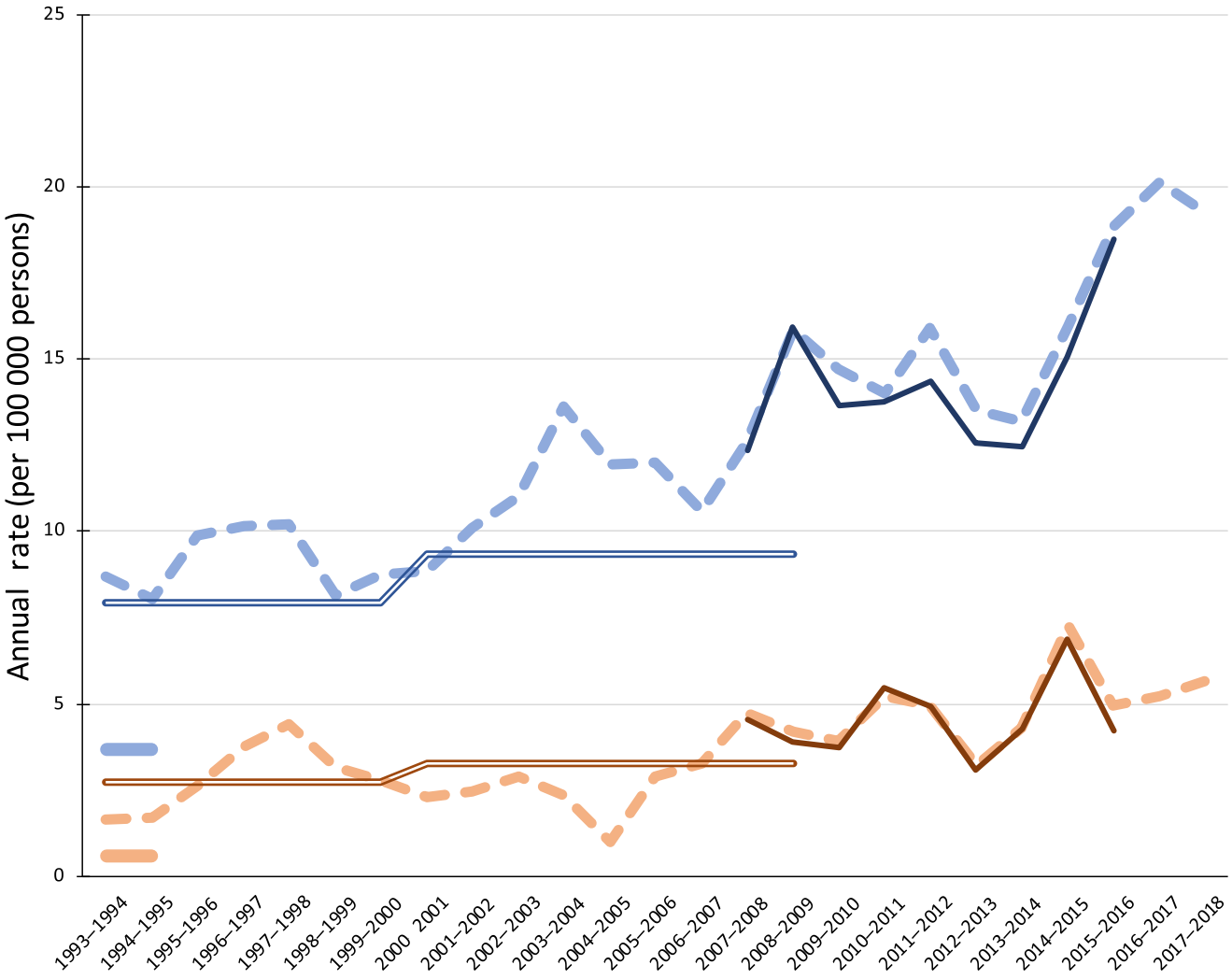

Fig 1 Hospitalisation rate and intravenous immunoglobulin (IVIG)-treatment rate of Kawasaki disease (KD) in Australia over 25 years, with comparison to published historical estimates of incidence. Comparison to previous published estimates of Australian KD incidence: Royle *et al.*[9] and Saundankar *et al.*[10] The study by Saundankar *et al.* was performed in only one Australian state – Western Australia. Hospitalisations data are from the National Hospital Morbidity Database – Australian Institute of Health and Welfare (NHMD). IVIG-treatment data are from the Supply Tracking Analysis Reporting System – Australian Red Cross Lifeblood (STARS). (), NHMD 0–4 years; (), STARS 0–4 years; (), Saundankar 0–4 years; (), Royle 0–4 years; (), NHMD 5–9 years; (), STARS 5–9 years; (), Saundankar 5–9 years; (), Royle 5–9 years.

Statistical analysis was performed using Stata/IC 15.1 for Mac (StataCorp 2017; Stata Statistical Software: Release 15, College Station, TX, USA). Confidence intervals for rates assume a Poisson distribution; binomial distribution was used for proportions. Seasonality was assessed using the Walter-Elwood test.[16] Ethical approval was granted by the Human Research Ethics Committee of Australian Red Cross Lifeblood (HREC 2015#12).

Results

STARS recorded 3176 doses of IVIG issued for the treatment of KD between January 2007 and June 2016, representing 2694 IVIG-treated episodes of KD in 2645 individuals. Of the 2694 IVIG-treated episodes of KD, 485 (18.0%) received two or more doses of IVIG within 30 days (IVIG retreatment). Of the 2645 individuals treated with IVIG, 33 (1.2%) had two or more discrete IVIG-treated episodes of KD (i.e. doses of IVIG for the treatment of KD separated by more than 30 days – classified as disease recurrence; see Methods for details). The STARS dataset overlapped with data published by Saundankar *et al.* for 3 years, during which there was close agreement (Table 1, Western Australia data only). The NHMD recorded 6395 episodes of care for KD between 1993 and 2017, representing 5949 KD hospitalisations.

There was close agreement between the IVIG treatment rate and the hospitalisation rate during the 9 years in which the STARS and NHMD datasets overlapped (Table 2, Fig. 1). In the 0- to 4-year age group, the IVIG-treatment rate was 14.31 per 100 000 person-years (95% confidence interval (CI) 13.67–14.97), and the hospitalisation rate was 14.99 per

Table 3 Kawasaki disease hospitalisation rate, by age: 1993–1997 to 2013–2017

Age group, years	Hospitalisation rate (per 100 000 person-years)					Mean annual increase
	1993–1997, rate (95% CI)	1998–2002, rate (95% CI)	2003–2007, rate (95% CI)	2008–2012, rate (95% CI)	2013–2017, rate (95% CI)	1993–2017, % (95% CI)
0–4	9.39 (8.66–10.16)	9.39 (8.65–10.17)	12.14 (11.31–13.02)	14.79 (13.91–15.70)	17.51 (16.59–18.47)	3.5 (2.9–4.1)
0–1	13.50 (11.57–15.67)	11.03 (9.27–13.03)	13.83 (11.89–16.00)	15.55 (13.61–17.70)	13.77 (11.98–15.75)	0.7 (−0.3–1.8)
1–4	8.37 (7.60–9.20)	8.99 (8.18–9.85)	11.71 (10.80–12.69)	14.59 (13.62–15.61)	18.44 (17.39–19.54)	4.3 (3.7–5.0)
5–9	2.85 (2.45–3.29)	2.72 (2.34–3.15)	3.23 (2.81–3.69)	4.31 (3.83–4.83)	5.49 (4.98–6.04)	4.0 (2.5–5.4)
10–14	0.28 (0.17–0.44)	0.51 (0.35–0.71)	0.51 (0.35–0.71)	0.76 (0.57–1.00)	0.72 (0.53–0.94)	4.5 (2.9–6.2)
15–19	0.05 (0.01–0.14)	0.09 (0.03–0.20)	0.12 (0.05–0.23)	0.07 (0.02–0.16)	0.15 (0.07–0.27)	4.2 (−0.1–8.6)

Hospitalizations data are from the National Hospital Morbidity Database of the Australian Institute of Health and Welfare. CI, confidence interval.

100 000 person-years (95% CI 14.33–15.66). Rates in the 5- to 9-year age group showed a similar level of agreement (Table 2).

Hospitalisation trends

Hospitalisation rates in the 0- to 4-year age group rose an average rate of 3.5% (95% CI 2.9–4.1) annually between 1993 and 2018, increasing from 9.39 per 100 000 person-years (95% CI 8.66–10.16) in 1993–1997 to 17.47 per 100 000 person-years in 2013–2017 (95% CI 16.59–18.47) (Table 3). Similar rates of growth were observed in the 5- to 9-year and 10- to 14-year age groups, but not in the 0- to 1-year or 15- to 19-year age group (Table 3). Hospitalisation rates by sex are provided in Table S2 (Supporting Information).

Age distribution

Differential rates of change in hospitalisation rates resulted in a changing age structure of KD hospitalisations over the five

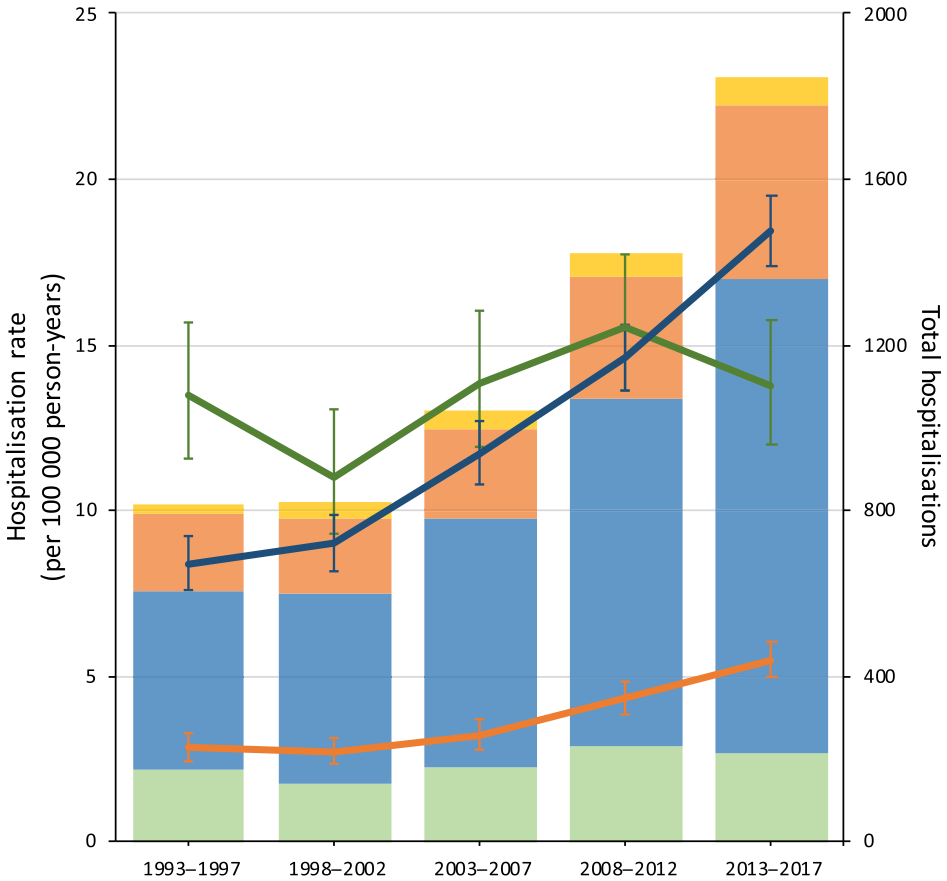

Fig 2 Kawasaki disease hospitalisations, by age: 1993–1997 to 2013–2017. Hospitalisations data are from the National Hospital Morbidity Database – Australian Institute of Health and Welfare. Intravenous immunoglobulin-treatment data are from the Supply Tracking Analysis Reporting System – Australian Red Cross Lifeblood. Data are from the National Hospital Morbidity Database – Australian Institute of Health and Welfare. For disaggregation by sex, see Figure S1a,b (Supporting Information). (), 0–1 years (*n*); (), 1–4 years (*n*); (), 5–9 years (*n*); (), ≥10 years (*n*); (), 0–1 years (rate); (), 1–4 years (rate); (), 5–9 years (rate).

periods, with a disproportionate increase in the 1- to 4-year age group (Fig. 2, Fig. S1a,b, Supporting Information). Detailed age structure was available from the STARS dataset (Fig. 3a,b), with the overall IVIG-treatment rate peaking in the second year of life (15.53 per 100 000 person-years, 95% CI 14.15–17.02).

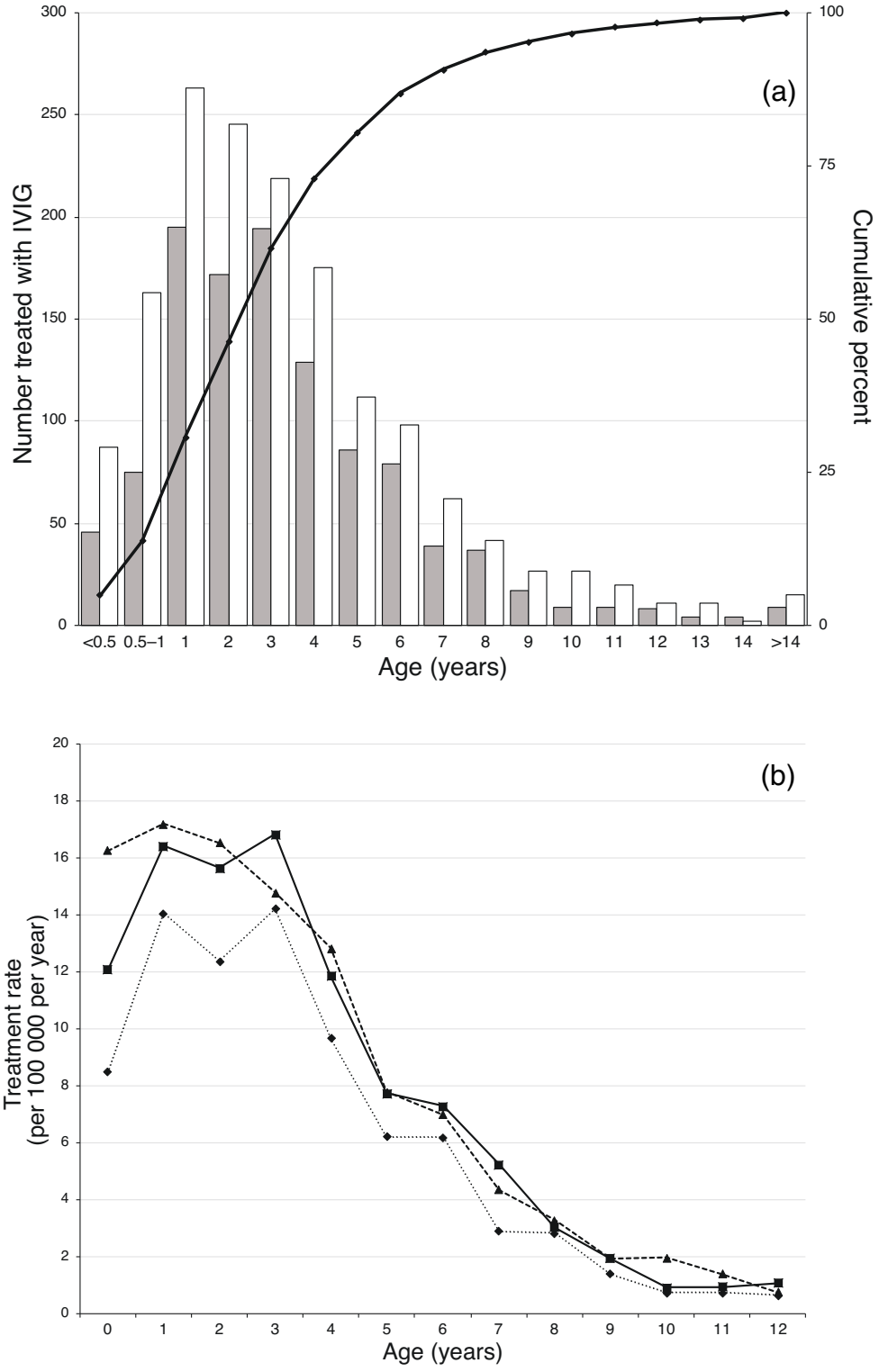

Fig 3 Treatment of Kawasaki disease with intravenous immunoglobulin (IVIG), by age – age distribution and age-specific treatment rate: January 2007 to July 2016. (a) Age distribution of 2694 individuals for whom IVIG was issued as treatment for their first episode of KD between January 2007 and July 2016. (b) Age-specific treatment rate of KD by single year of age. IVIG-treatment data are from the Supply Tracking Analysis Reporting System – Australian Red Cross Lifeblood. (a) (▣), Female; (□), male. (b) (—■—), All; (- -▲- -), male; (···◆···), female.

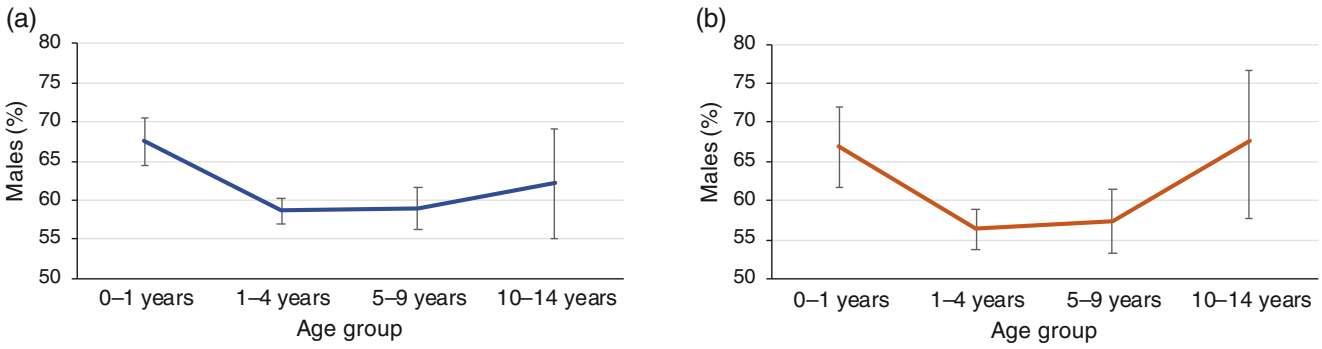

Fig 4 Males as a percentage of total Kawasaki disease numbers, by age: comparison of two datasets. (a) Hospitalisations data are from the National Hospital Morbidity Database – Australian Institute of Health and Welfare (NHMD). (b) Intravenous immunoglobulin-treatment data are from the Supply Tracking Analysis Reporting System – Australian Red Cross Lifeblood (STARS). Bars represent 95% confidence interval assuming a binomial distribution.

Sex distribution

Males outnumbered females in all age groups in both datasets (Fig. 3 and Fig. S1, Supporting Information), comprising 60.3% all KD hospitalisations (95% CI 59.0–61.5) and 58.5% of all IVIG-treated episodes (95% CI 56.6–60.4). Male to female ratios varied by age in both datasets (Fig. 4, Table S3, Supporting Information), with the male predominance higher in the 0- to 1-year age group than other groups.

Seasonal variation

There was some evidence of seasonal variation in KD diagnosis, with higher average monthly treatment rates in the second half of the year compared with the first (18.9 episodes per month between July and December vs. 14.6 per month between January and June; $P < 0.001$). Seasonal variation was poorly modelled by a sinusoidal function (Walter Elwood tests

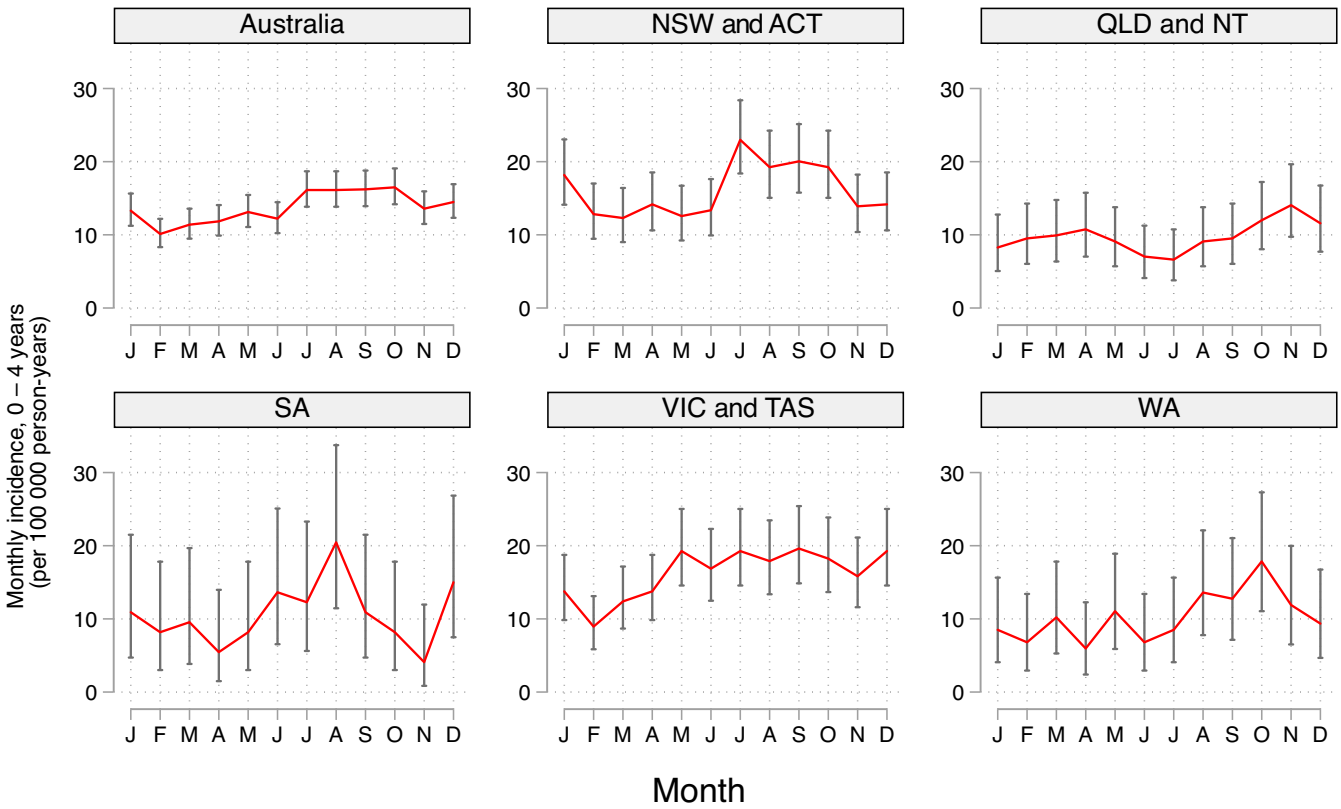

Fig 5 Monthly variation of Kawasaki disease treatment rates in Australia, by region: 2007–2015. Intravenous immunoglobulin-treatment data are from the Supply Tracking Analysis Reporting System – Australian Red Cross Lifeblood. Bars represent 95% confidence interval (CI) assuming a binomial distribution. For plots of individual years, see Figure S2a–f (Supporting Information). (——), Rate; (⟵⟶), 95% CI.

$P < 0.001$, peak mid-September – Southern Hemisphere Spring). This pattern varied across Australia; a unimodal distribution was observed in temperate south-eastern states (e.g. Victoria, New South Wales), with peak incidence between August and October. There was some indication of a bimodal distribution in the tropical northern states (e.g. Queensland and New Territory), with smaller peaks occurring in April and December. (Fig. 5, Table S4 and Fig. 2a–f, Supporting Information)

Discussion

We used two independent national datasets to derive the most rigorous estimate of KD incidence in Australia to date. For the period 2007–2015, we were able to accurately determine both the IVIG-treatment rate and the KD hospitalisation rate, which we believe provide lower and upper bounds of the true diagnosis rate, respectively. We then extended our analyses of both datasets, describing trends in hospitalisations over 25 years and seasonal variation in the IVIG-treatment rates by region.

During the 9 years in which the datasets overlapped, the treatment rate of KD with IVIG was 14.31 per 100 000 person-years in the 0- to 4-year age group (95% CI 13.67–14.97), while the hospitalisation rate in the same age group was 14.99 per 100 000 person-years (95% CI 14.33–15.66). This is markedly higher than the previous estimate of Australian incidence of 9.34 per 100 000 person-years,[10] suggesting that the incidence of KD in Australia is approaching that reported in the USA (20.8 per 100 000 *per annum*)[17] and Canada (20.5 per 100 000 *per annum*),[18] and is considerably higher than that reported most recently in the UK (8.39 per 100 000 *per annum*).[19]

We observed a mean annual increase in the KD hospitalisation rate of 3.5% in the 0- to 4-year age group over 25 years. This increase occurred primarily in the 1- to 4-year age group, which replaced the 0- to 1-year age group as the age group with the highest incidence of KD – a phenomenon not previously reported elsewhere. It is unclear whether this change in KD hospitalisations reflects a true increase in disease incidence, increasing recognition and/or diagnosis, or both. Increasing KD incidence has been inconsistently reported around the world. Data from Japan are the most convincing; with increasing incidence consistently reported from hospital-based surveys for almost 40 years, albeit with response rates below 75%.[20] Evidence of increasing incidence in other regions is less clear.[5,6,8] It is notable that the period of this study also saw significant changes in Australia's demographic structure, with the proportion of Australian residents born in Asia increasing from 5% in 1996 to over 12% in 2019[21]; however, the possible influence of this demographic change could not be assessed in this study.

We observed an overall male to female ratio of 1.52:1 – similar to previously reported data[1] – however, this varied by age, with an exaggerated male predominance in the 0- to 1-year and 10- to 14-year age groups (2.08:1 and 1.65:1, respectively). Advani *et al.* reported a male to female ratio of 4:1 among adolescents,[22] however the phenomenon has not previously been reported in the 0- to 1-year age group (although it is evident in data published by Makino *et al.*[20]).

We observed a peak in the IVIG treatment rate in September (Southern Hemisphere spring) nationally, although the seasonal patterns differed between the temperate south-eastern states – which had a unimodal distribution, and the tropical northern states – which had a bimodal distribution. Globally, there is wide variation in the reported seasonality of KD.[23] While there are few data on KD seasonality in the Southern Hemisphere, our observation of a peak in September is similar to that reported in New Zealand.[24]

Studies of disease incidence typically take one of two approaches to case definition: the 'formal' approach where the unit of measure is cases fulfilling strict diagnostic criteria, or the 'pragmatic' approach, where the unit of measure is physician-made diagnoses. While the formal approach is rigorous, limitations arise when the boundaries of the disease expand beyond the defined criteria, as is the case for KD. A pragmatic approach has commonly been taken in KD research – using the diagnosis rate as a surrogate for incidence and estimating the diagnosis rate from the hospitalisation rate. This approach leverages the availability of large administrative datasets reporting hospitalisations, but has been shown to overestimate true KD numbers.[11,25] We sought to address this bias by using the rate of IVIG treatment as a second measure of the diagnosis rate. This novel approach was possible as Australia has a single centralised provider of publicly funded immunoglobulin, and the concordant results increase our confidence in the estimate of the incidence rate.

We acknowledge a number of important limitations to this approach. We retrospectively analysed administrative datasets that were not originally established for research and therefore the analysis involved a number of assumptions. We considered all hospital-based episodes of care for KD requiring at least 1-night admission in KD hospitalisation. Children treated as outpatients would have been systematically excluded from this study; however, this would be rare as Australian practice throughout the study period was for inpatient management. We were unable to account for children having multiple hospitalisations within the same episode of KD (as might occur in treatment-resistant disease). We addressed this bias in the STARS dataset by defining a 30-day cut-off within which retreatment constituted resistance and after which constituted disease recurrence. We were unable to comment on issues of diagnostic error or misclassification. We sought to address this by comparing our estimates of the IVIG treatment rate with estimates derived from data by Saundankar *et al.* that used a formal case definition for KD; this was applied by reviewing individual patient medical records. Estimates from both datasets were similar in the overlapping years.

This study has several key strengths related to the completeness and quality of the data sources. Australia has a publicly funded universal health-care system (Medicare) that provides free treatment in public hospitals to citizens and most residents; data about hospitalisations are therefore unlikely to be biassed by issues of inequitable access to health care. Additionally, coding of discharge diagnosis is standardised for the purpose of hospital funding, ensuring a high level of data quality. Consequently, our estimate of the hospitalisation rate is likely to be accurate. Our estimate of the IVIG treatment rate used data from Australia's sole provider of publicly funded blood products – Australian Red Cross Lifeblood. The STARS database has previously been validated for accuracy and completeness of data; estimates of the IVIG treatment rate are therefore also likely to be accurate.

Conclusions

We describe a novel approach to the investigation of KD epidemiology and report an increasing incidence of KD in Australia. High-quality, standardised prospective surveillance is warranted to understand the evolving epidemiology of KD in Australia and elsewhere to inform clinical and scientific priorities.

Acknowledgements

This research was made possible by the provision of data by Australian Red Cross Lifeblood. Australian governments fund Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian community. We acknowledge the support of the data custodians in facilitating access to these data. We are also grateful to Dr Saundankar (Great Ormond Street Children's Hospital, Formerly of Children's Cardiac Centre, Princess Margaret Hospital for Children, Perth, Western Australia, Australia), for providing access to data from her study into the epidemiology of KD in Western Australia. This study was supported by a National Blood Sector Research and Development Pilot Project grant (ID111) from the National Blood Authority of Australia. D Burgner and E Wood are supported by National Health and Medical Research Council (NHMRC) Investigator Grants. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript, nor the decision to submit the manuscript for publication.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Supplementary methods.
Table S1. Total numbers of Kawasaki disease hospitalisations and IVIG-treated episodes, by age and sex: 1993–1997 to 2013–2017.

Table S2. Kawasaki disease hospitalisation rates and IVIG-treatment rates, by age and sex: 1993–1997 to 2013–2017.

Table S3. Males as a percentage of total Kawasaki disease hospitalisation and IVIG-treated episodes, by age: 1993–1997 to 2013–2017.

Table S4. Walter-Elwood test of annual periodicity for Australia and five sub-regions.

Fig. S1. Kawasaki disease hospitalisations, by age (a, males; b, females): 1993–1997 to 2013–2017.

Fig. S2. Monthly variation of Kawasaki disease treatment rates in Australia, by region: 2007 to 2015 – (a) All of Australia; (b) New South Wales and the Australian Capital Territory; (c) Queensland and the Northern Territory; (d) South Australia; (e) Victoria and Tasmania; (f) Western Australia.

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Epidemiology of Kawasaki disease in Australia using two nationally complete datasets

Supplementary Methods

We analysed two national administrative datasets relevant to KD in Australia. Hospitalisations were derived from the National Hospital Morbidity Database (NHMD), while immunoglobulin treatment was derived from the Supply Tracking Analysis Reporting System (STARS). These datasets overlapped in time allowing for comparison and cross-validation. The NHMD provided 25 years of aggregated data, whereas STARS provided individual-level data over nine years.

NHMD

The NHMD is a database of "separations" at Australian hospitals, both public and private, from July 1993. A separation is defined as:

> *An episode of care for an admitted patient, which can be a total hospital stay (from admission to discharge, transfer or death) or a portion of a hospital stay beginning or ending in a change of type of care (for example, from acute care to rehabilitation). Separation also means the process by which an admitted patient completes an episode of care either by being discharged, dying, transferring to another hospital or changing type of care.*[1]

The NHMD is made publicly available by the Australian Institute of Health and Welfare.[2] Separation numbers are provided in aggregated form for each Australian financial year, beginning July 1st 1993 (Australian financial years run from July 1st to the following June 30th, and are labelled for the calendar year in which they begin–the 1993 financial year begins on July 1st 1993). Data can be disaggregated by discharge diagnosis, sex, and age bracket (less than 1 year, 1 to 4 years, and 5-year brackets thereafter). Data cannot be disaggregated by jurisdiction or by month.

We retrieved annual KD separation numbers using discharge diagnosis codes (International Classification of Disease 9–Clinical Modification [ICD-9-CM] 446.1 to 1997-98 and ICD-10–Australian Modification [ICD-10-AM] M30.3 thereafter). In order to derive data correlating with discrete clinical episodes of KD we excluded "same-day separations" and analysed only those separations involving at least one overnight stay–we describe these encounters as "hospitalisations". This was based on Australian practice to admit children

with acute KD overnight for observation and treatment (such as with an infusion of intravenous immunoglobulin–IVIG). Same-day separations were excluded on the basis that they were unlikely to correlate with a discrete episode of KD. Same-day separations may result if a child is admitted to a day-stay unit for IVIG infusion, however we do not believe that this occurs in practice. Same-day separations may otherwise be generated in the course of an admission that included a short transfer to another institution. For example: a child admitted to a metropolitan hospital with a diagnosis of KD might be transferred to a quaternary paediatric centre for a cardiology review and echocardiogram, before returning to the referring hospital on the same day. In this example the same-day separation recorded at the quaternary centre ought not be considered an episode of KD.

STARS

IVIG at a dose of 2 grams per kilogram bodyweight significantly reduces the incidence of coronary artery aneurysms in patients with KD,[3] and is recommended as first-line treatment.[4] The Australian Red Cross Lifeblood (previously the Australian Red Cross Blood Service) is the sole provider of publicly funded blood products in Australia. STARS was an inventory management system used by the Australian Red Cross Lifeblood for the approval, tracking and distribution of immunoglobulin products from 2006 to 2016. It had previously been validated for accuracy and completeness of data. Strict criteria govern access to publicly funded immunoglobulin,[5] with KD an approved indication since the first guidelines in 1993.[6] For these reasons, we can be confident that all KD cases receiving IVIG during the study period would have been captured in the STARS database.

We retrieved all allocations of IVIG for KD recorded in STARS from January 2007 to June 2016. Each dose had the following metadata: patient record number, name, date of birth, sex, and weight; IVIG dose and brand; and the request date and delivery hospital. All records were reviewed by hand to identify errors, such as:

- Patients entered more than once but with different record numbers. This occurred occasionally if a name was misspelled, or if a subsequent request came from a different hospital. Patient date of birth, weight, and physical location were used to re-assign these doses and, where possible, hospital records departments were contacted to confirm the accuracy of patient details.
- Multiple doses dispatched but not give. This sometimes occurs if a vial of IVIG that had been allocated to a patient was not able to be given (i.e. it broke or expired). This was usually recorded in the comment section of STARS by Lifeblood staff.

- Patients entered without a sex. Where possible this was confirmed with the records department of the relevant hospital; one record was not able to be accurately allocated a sex.
- Patients entered with incorrect date of birth. This was suspected when the weight recorded or dose allocated was implausible at the age provided. Where possible this was confirmed by calling the records department of the relevant hospital.

The resulting dataset comprised 3,176 unique doses of IVIG allocated for the treatment of IVIG between January 2007 and June 2016. Two clinical phenomena complicated the interpretation of this dataset: IVIG-resistant KD and recurrent KD. In IVIG-resistant KD there is a state of ongoing inflammation after the first dose of IVIG; provision of a second dose of IVIG is a common approach to managing this condition. Recurrent KD occurs when an individual who has previously had KD is diagnosed with KD again, with the underlying assumption of an intervening state of normalcy without systemic inflammation. In both of these scenarios an individual might receive multiple doses of IVIG; in the former these should be interpreted as representing a single 'episode' of KD, whereas in the latter they represent multiple discrete episodes. Unfortunately there is no consensus definition of KD recurrence.[7–9] We therefore employed a 30-day cut-off such that IVIG doses issued within 30 days constituted retreatment for one episode of KD, whereas doses after 30 days constituted a new episode of KD. This 30 day period was re-calculated for each dose, such that 3 doses given over 40 days but each only 20 days apart would all be considered one episode of KD, whereas 2 doses given 40 days apart would be considered separate episodes.

For comparison with data published by Saundankar, *et al* KD numbers in STARS were analysed by calendar years. In contrast when KD numbers were compared with those from the NHMD they were analysed by Australian financial years (July 1st to June 30th). Finally, for seasonal analysis using the Walter-Elwood test KD numbers were analysed by calendar month.

Dataset Comparison

Data linkage between these datasets was not possible due to the aggregated nature of the NHMD. Age-specific incidence rates were calculated from both datasets. Historical age-specific population estimates were obtained from publicly available census data from the Australian Bureau of Statistics.[10] Incidence rates are presented graphically by year, but are summarised as average annualised rates for five 5-year periods: Period 1 (1993–1997), Period 2 (1998–2002), Period 3 (2003–2007), Period 4 (2008–2012), and Period 5 (2013–2017). The NHMD and STARS overlapped fully for Period 4.

Statistical Analysis

Statistical analysis was performed using Stata/IC 15.1 for Mac (StataCorp 2017. Stata Statistical Software: Release 15. College Station, Texas). Confidence intervals for rates assume a Poisson distribution, binomial distribution was assumed for proportions. Seasonality was assessed using the Walter-Elwood test,[11] utilising the user-written command `seast` (authors Pearce MS and Feltbower R). The Walter-Elwood test plots case numbers over a unit circle representing the year; annual variation results in the displacement of the centre of the plot from the centre of the unit circle. The vector so derived has both magnitude and direction (measured in degrees: θ°). The magnitude represents the amplitude of annual variance, whereas θ corresponds to the point in the calendar at which the maximal amplitude occurs. This is assessed using a χ^2 goodness-of-fit test.

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Epidemiology of Kawasaki disease in Australia using two nationally complete datasets

Supplementary Results

Tables

Table 4.S1: Total Numbers of Kawasaki Disease Hospitalisations and IVIG-Treated Episodes, by Age and Sex: 1993–1997 to 2013–2017

	1993–1997	1998–2002	2003–2007	2008–2012		2013–2017
Data source	**NHMD**	**NHMD**	**NHMD**	**NHMD**	**STARS**	**NHMD**
Both						
0–4 years	607	599	783	1,067	1,012	1,360
0–1 years	173	138	181	230	202	213
1–4 years	434	461	602	837	810	1,147
5–9 years	184	182	214	295	288	420
10–14 years	18	34	35	53	57	51
15–19 years	3	6	8	5	7	11
≥20 years	4	1	2	3	4	4
Total	**816**	**822**	**1,042**	**1,423**	**1,368***	**1,846**
Males						
0–4 years	405	358	484	615	579	809
0–1 years	130	85	133	147	132	136
1–4 years	275	273	351	468	447	673
5–9 years	94	103	140	181	166	246
10–14 years	11	23	20	28	36	37
15–19 years	2	5	6	5	6	5
≥20 years	1	0	1	2	3	4
Total	**513**	**489**	**651**	**831**	**790**	**1,101**
Females						
0–4 years	202	241	299	452	432	551
0–1 years	43	53	48	83	70	77
1–4 years	159	188	251	369	362	474
5–9 years	90	79	74	114	122	174
10–14 years	7	11	15	25	21	14
15–19 years	1	1	2	0	1	6
≥20 years	3	1	0	1	1	0
Total	**303**	**333**	**391**	**592**	**577**	**745**

Datasets overlapped for 9 complete years, from July 2007 to June 2016; STARS data here only shown for the 2008–2012 period. *One record did not have sex allocated.

Abbreviations: NHMD, National Hospital Morbidity Database–Australian Institute of Health and Welfare; STARS, Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Table 4.S2: Kawasaki Disease Hospitalisation Rates and IVIG-Treatment Rates, by Age and Sex: 1993–1997 to 2013–2017

	1993–1997	1998–2002	2003–2007	2008–2012		2013–2017
Data source	**NHMD**	**NHMD**	**NHMD**	**NHMD**	**STARS**	**NHMD**
All						
0–4 years	9.39 (8.66–10.16)	9.39 (8.65–10.17)	12.14 (11.31–13.02)	14.79 (13.91–15.70)	14.03 (13.17–14.92)	17.51 (16.59–18.47)
0–1 years	13.50 (11.57–15.67)	11.03 (9.27–13.03)	13.83 (11.89–16.00)	15.55 (13.61–17.70)	13.66 (11.84–15.68)	13.77 (11.98–15.75)
1–4 years	8.37 (7.60–9.20)	8.99 (8.18–9.85)	11.71 (10.80–12.69)	14.59 (13.62–15.61)	14.12 (13.16–15.13)	18.44 (17.39–19.54)
5–9 years	2.85 (2.45–3.29)	2.72 (2.34–3.15)	3.23 (2.81–3.69)	4.31 (3.83–4.83)	4.21 (3.73–4.72)	5.49 (4.98–6.04)
10–14 years	0.28 (0.17–0.44)	0.51 (0.35–0.71)	0.51 (0.35–0.71)	0.76 (0.57–1.00)	0.82 (0.62–1.07)	0.72 (0.53–0.94)
15–19 years	0.05 (0.01–0.14)	0.09 (0.03–0.20)	0.12 (0.05–0.23)	0.07 (0.02–0.16)	0.10 (0.04–0.20)	0.15 (0.07–0.27)
Males						
0–4 years	12.21 (11.05–13.46)	10.94 (9.83–12.13)	14.63 (13.35–15.99)	16.60 (15.32–17.97)	15.63 (14.38–16.96)	20.29 (18.91–21.73)
0–1 years	19.77 (16.52–23.48)	13.25 (10.58–16.38)	19.78 (16.56–23.44)	19.36 (16.35–22.75)	17.38 (14.54–20.61)	17.12 (14.36–20.25)
1–4 years	10.34 (9.15–11.63)	10.37 (9.18–11.68)	13.31 (11.96–14.78)	15.89 (14.48–17.40)	15.18 (13.80–16.65)	21.08 (19.51–22.73)
5–9 years	2.84 (2.30–3.48)	3.01 (2.45–3.64)	4.12 (3.47–4.86)	5.15 (4.43–5.96)	4.73 (4.03–5.50)	6.27 (5.51–7.10)
10–14 years	0.33 (0.17–0.60)	0.68 (0.43–1.01)	0.56 (0.34–0.87)	0.79 (0.52–1.14)	1.01 (0.71–1.40)	1.01 (0.71–1.40)
15–19 years	0.06 (0.01–0.22)	0.15 (0.05–0.35)	0.17 (0.06–0.37)	0.13 (0.04–0.31)	0.16 (0.06–0.35)	0.13 (0.04–0.31)
Females						
0–4 years	6.42 (5.56–7.36)	7.75 (6.81–8.80)	9.53 (8.48–10.67)	12.87 (11.71–14.12)	12.30 (11.17–13.52)	14.58 (13.39–15.85)
0–1 years	6.90 (4.99–9.29)	8.69 (6.51–11.37)	7.54 (5.56–10.00)	11.53 (9.19–14.30)	9.73 (7.58–12.29)	10.24 (8.08–12.79)
1–4 years	6.30 (5.36–7.36)	7.53 (6.49–8.68)	10.03 (8.83–11.35)	13.22 (11.90–14.64)	12.97 (11.67–14.37)	15.66 (14.28–17.13)
5–9 years	2.86 (2.30–3.51)	2.43 (1.92–3.03)	2.29 (1.80–2.88)	3.42 (2.82–4.11)	3.66 (3.04–4.37)	4.68 (4.01–5.43)
10–14 years	0.22 (0.09–0.46)	0.34 (0.17–0.61)	0.45 (0.25–0.74)	0.74 (0.48–1.09)	0.62 (0.39–0.95)	0.40 (0.22–0.68)
15–19 years	0.03 (0.00–0.18)	0.03 (0.00–0.17)	0.06 (0.01–0.21)	0.00 (0.00–0.10)	0.03 (0.00–0.16)	0.17 (0.06–0.36)

Rates given as cases per 100,000 person-years. Datasets overlapped for 9 complete years, from July 2007 to June 2016; STARS data here only shown for the 2008–2012 period.
Abbreviations: NHMD, National Hospital Morbidity Database–Australian Institute of Health and Welfare; STARS, Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Table 4.S3: Males as a Percentage of Total Kawasaki Disease Hospitalisation and IVIG-Treated Episodes, by Age: 1993–1997 to 2013–2017

	1993–1997	1998–2002	2003–2007	2008–2012		2013–2017
Data source	**NHMD**	**NHMD**	**NHMD**	**NHMD**	**STARS**	**NHMD**
0–4 years	66.7 (62.9–70.4)	59.8 (55.8–63.6)	61.8 (58.4–65.2)	57.6 (54.7–60.6)	57.2 (54.1–60.2)	59.5 (56.9–62.1)
0–1 years	75.1 (68.2–81.0)	61.6 (53.3–69.3)	73.5 (66.6–79.4)	63.9 (57.5–69.8)	65.3 (58.5–71.6)	63.8 (57.2–70.0)
1–4 years	63.4 (58.7–67.8)	59.2 (54.7–63.6)	58.3 (54.3–62.2)	55.9 (52.5–59.2)	55.2 (51.7–58.6)	58.7 (55.8–61.5)
5–9 years	51.1 (43.9–58.2)	56.6 (49.3–63.6)	65.4 (58.8–71.5)	61.4 (55.7–66.7)	57.6 (51.9–63.2)	58.6 (53.8–63.2)
10–14 years	61.1 (38.5–79.8)	67.6 (50.7–81.0)	57.1 (40.8–72.0)	52.8 (39.7–65.6)	63.2 (50.2–74.5)	72.5 (59.0–83.0)

Datasets overlapped for 9 complete years, from July 2007 to June 2016; STARS data here only shown for the 2008–2012 period.
Abbreviations: NHMD, National Hospital Morbidity Database–Australian Institute of Health and Welfare (hospitalisations); STARS, Supply Tracking and Reporting System–Australian Red Cross Lifeblood (IVIG-treated episodes).

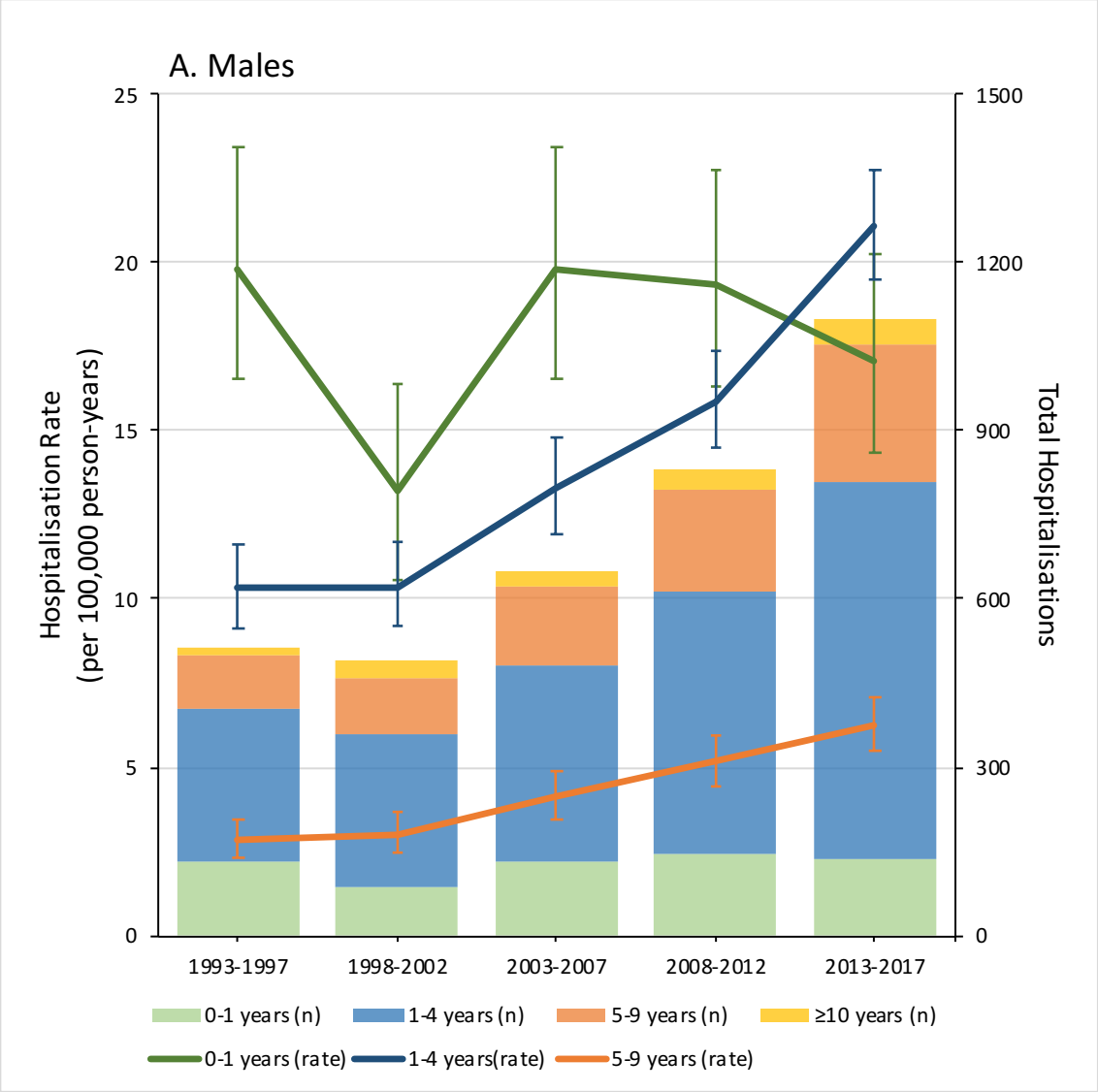
Table 4.S4: Walter-Elwood Test of Annual Periodicity for Australia and Five Sub-Regions.

Region	Walter Elwood p	Angle	Month	Amplitude
All Australia	<0.001	254°	September	0.2
NSW & ACT	<0.001	249°	September	0.2
QLD & NT	<0.001	339°	December	0.3
SA	0.276	210°	August	0.2
VIC & TAS	<0.001	234°	August	0.2
WA	<0.001	274°	October	0.5

Data from the Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

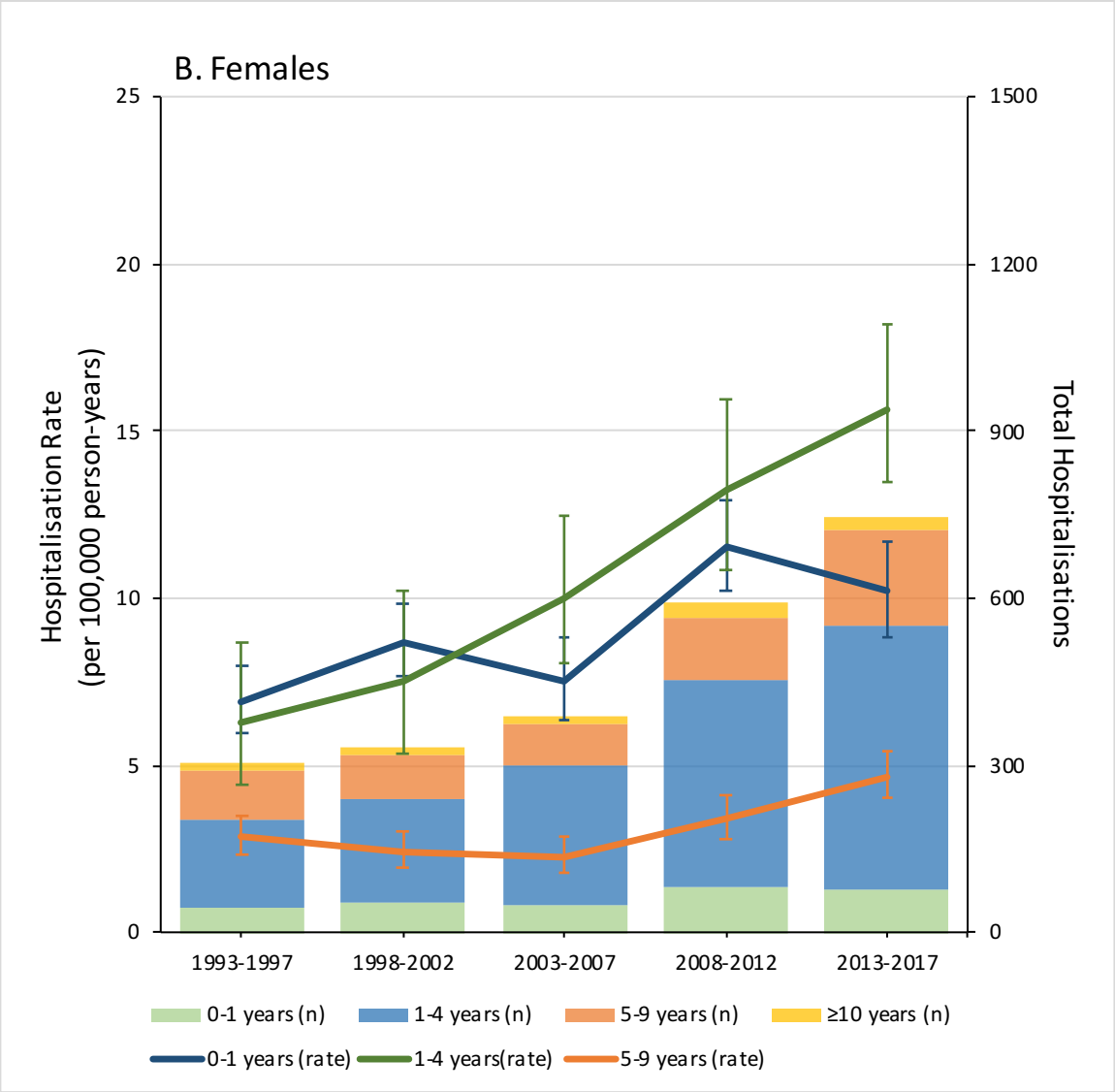
Figures

Figure 4.S1a: Kawasaki Disease Hospitalisations, by Age (Males): 1993–1997 to 2013–2017



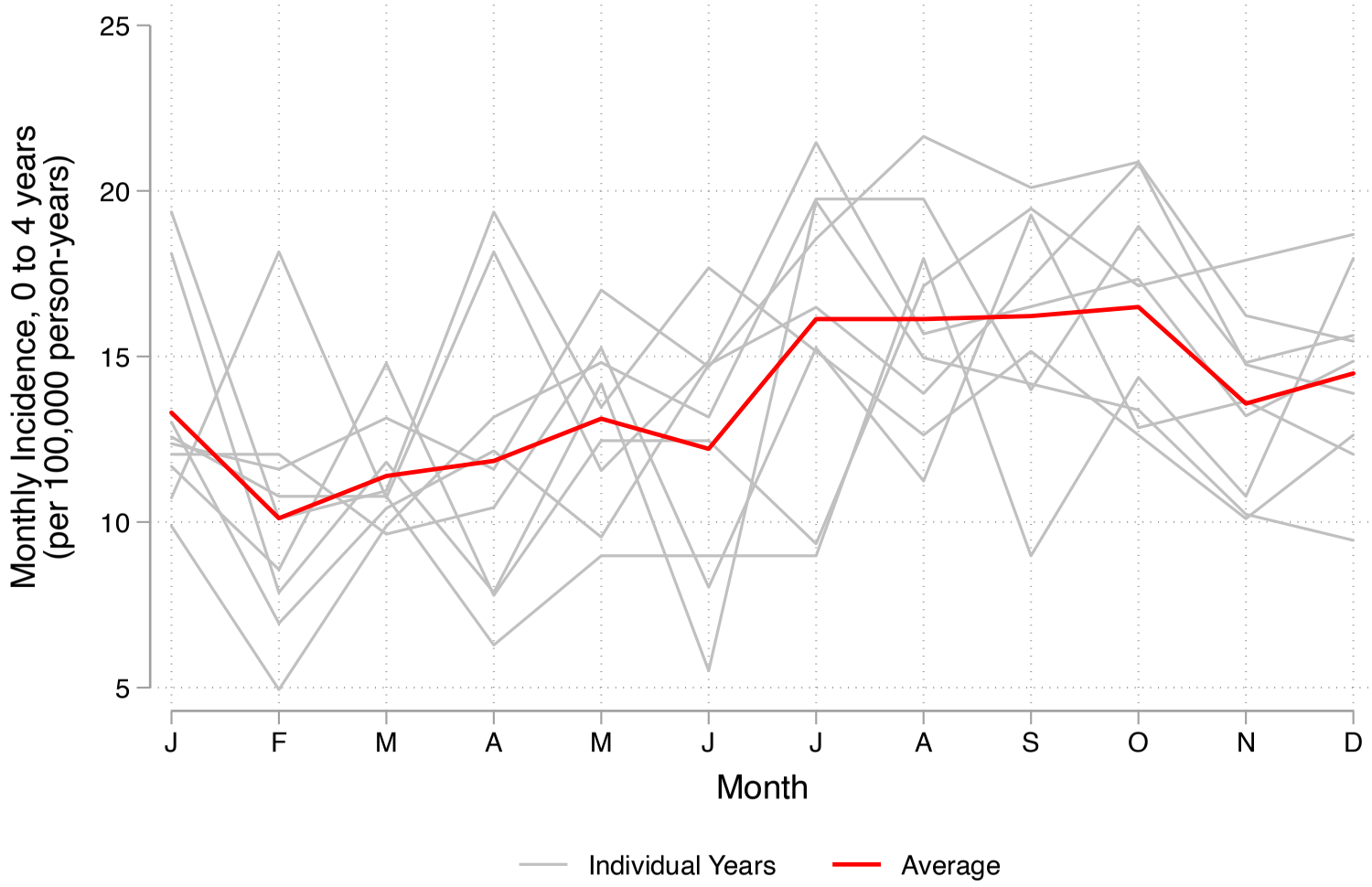
Data from the National Hospital Morbidity Database–Australian Institute of Health and Welfare.
Bars represent 95% confidence intervals.

Figure 4.S1b: Kawasaki Disease Hospitalisations, by Age (Females): 1993–1997 to 2013–2017



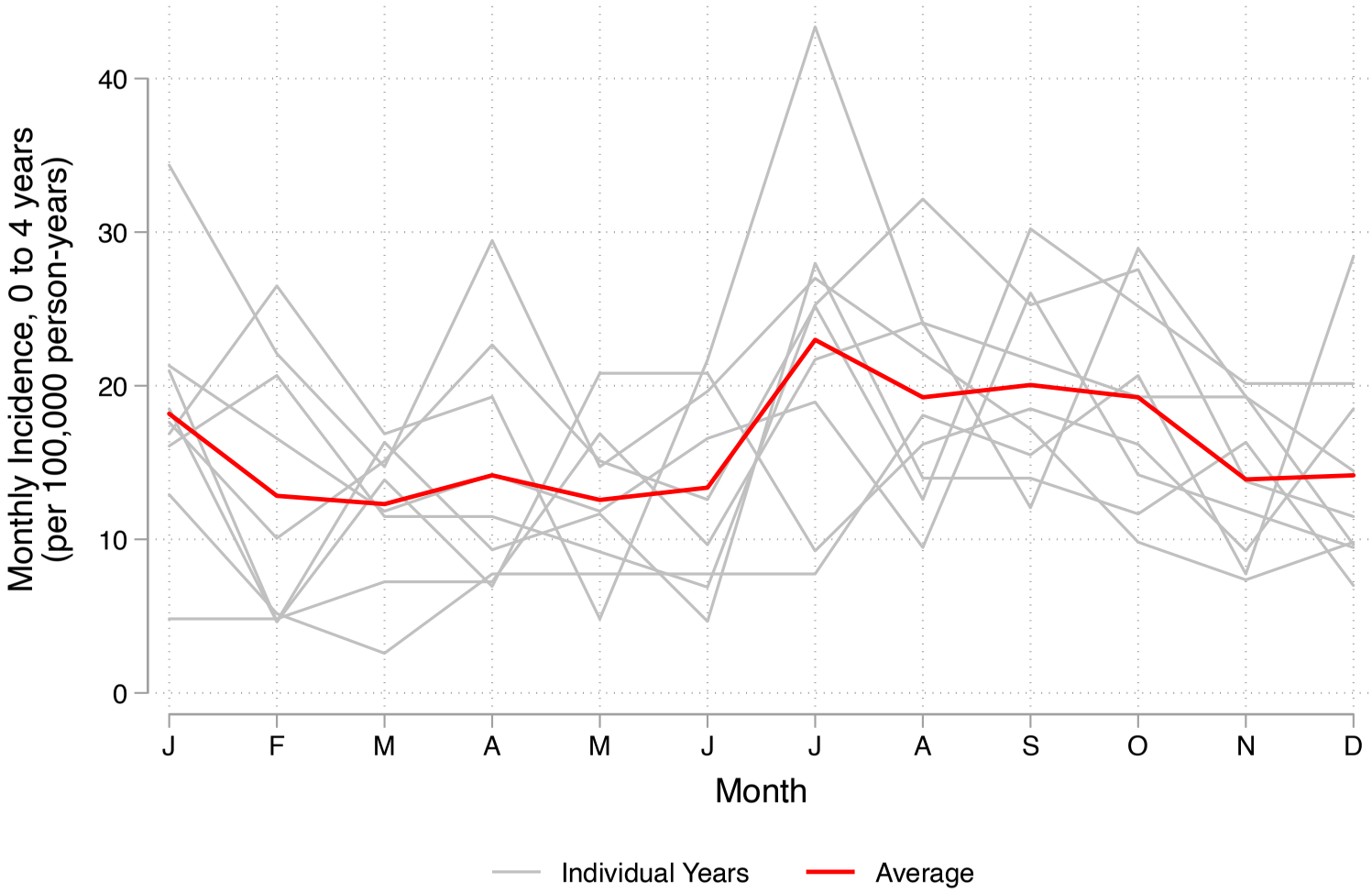
Data from the National Hospital Morbidity Database–Australian Institute of Health and Welfare.
Bars represent 95% confidence intervals.

Figure 4.S2a: Monthly Variation of Kawasaki Disease Treatment Rates in Australia, by Region: 2007–2015, All of Australia



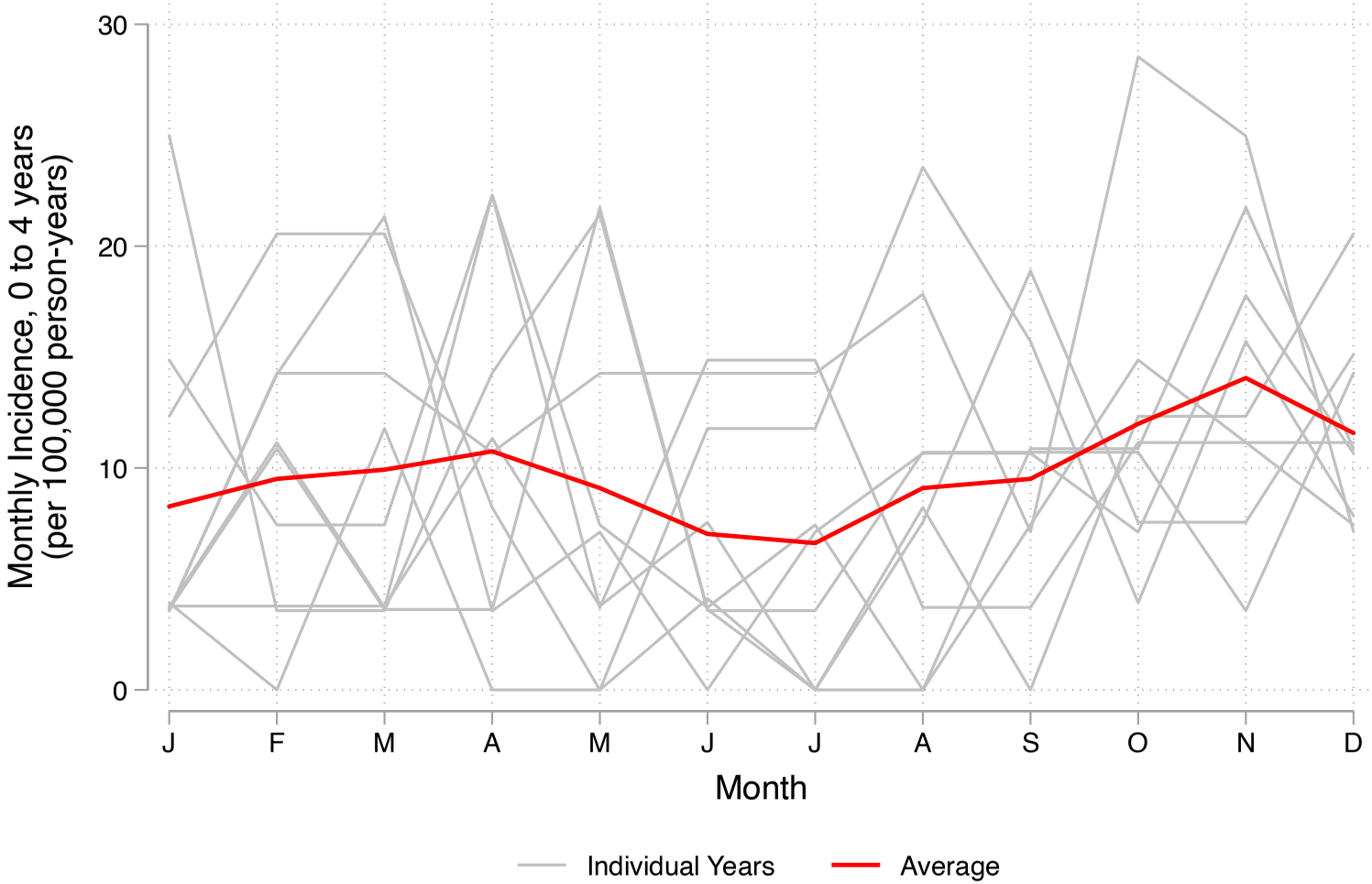
Data from the Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Figure 4.S2b: Monthly Variation of Kawasaki Disease Treatment Rates in Australia, by Region: 2007–2015, New South Wales and the Australian Capital Territory



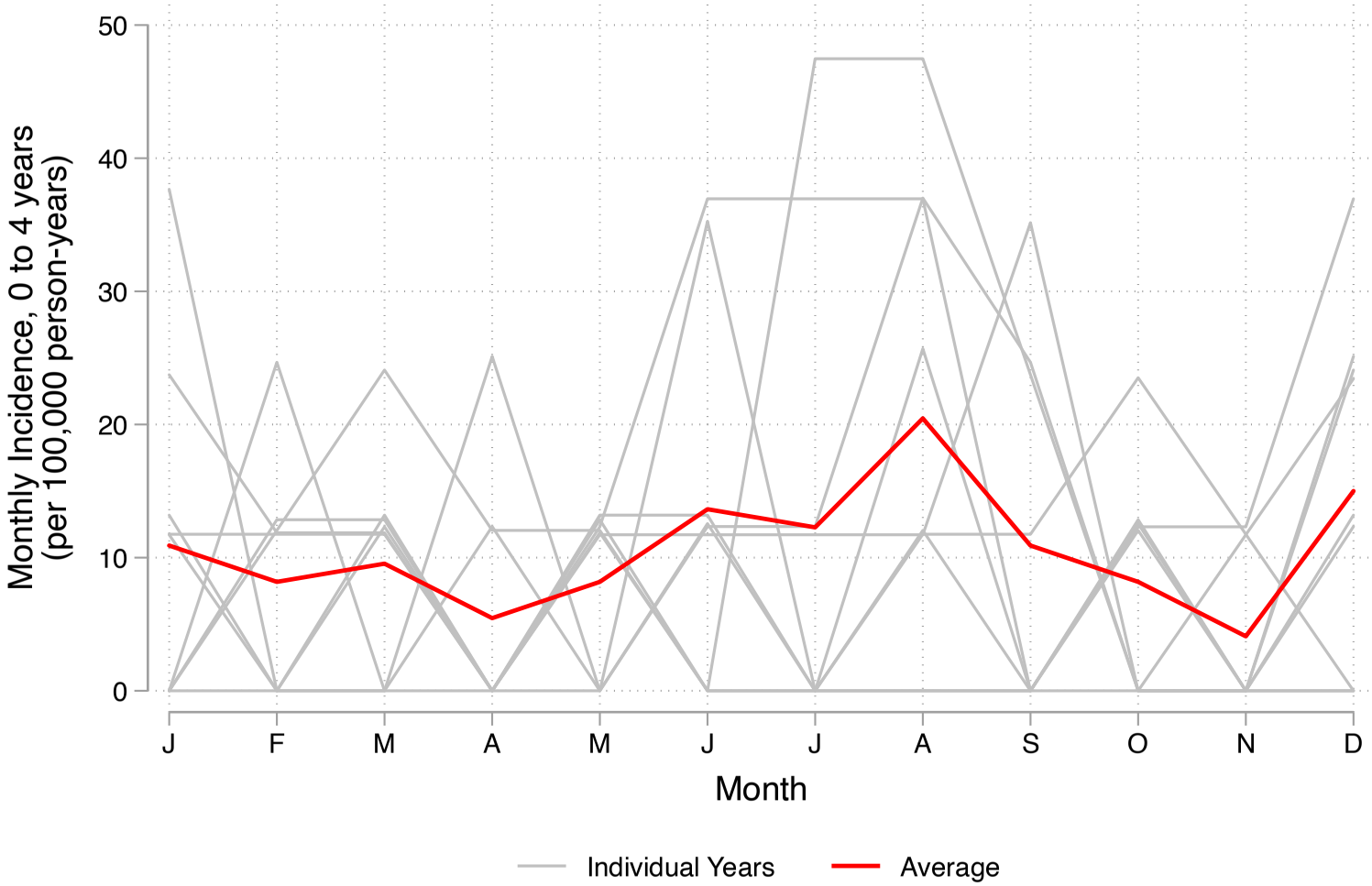
Data from the Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Figure 4.S2c: Monthly Variation of Kawasaki Disease Treatment Rates in Australia, by Region: 2007–2015, Queensland and the Northern Territory



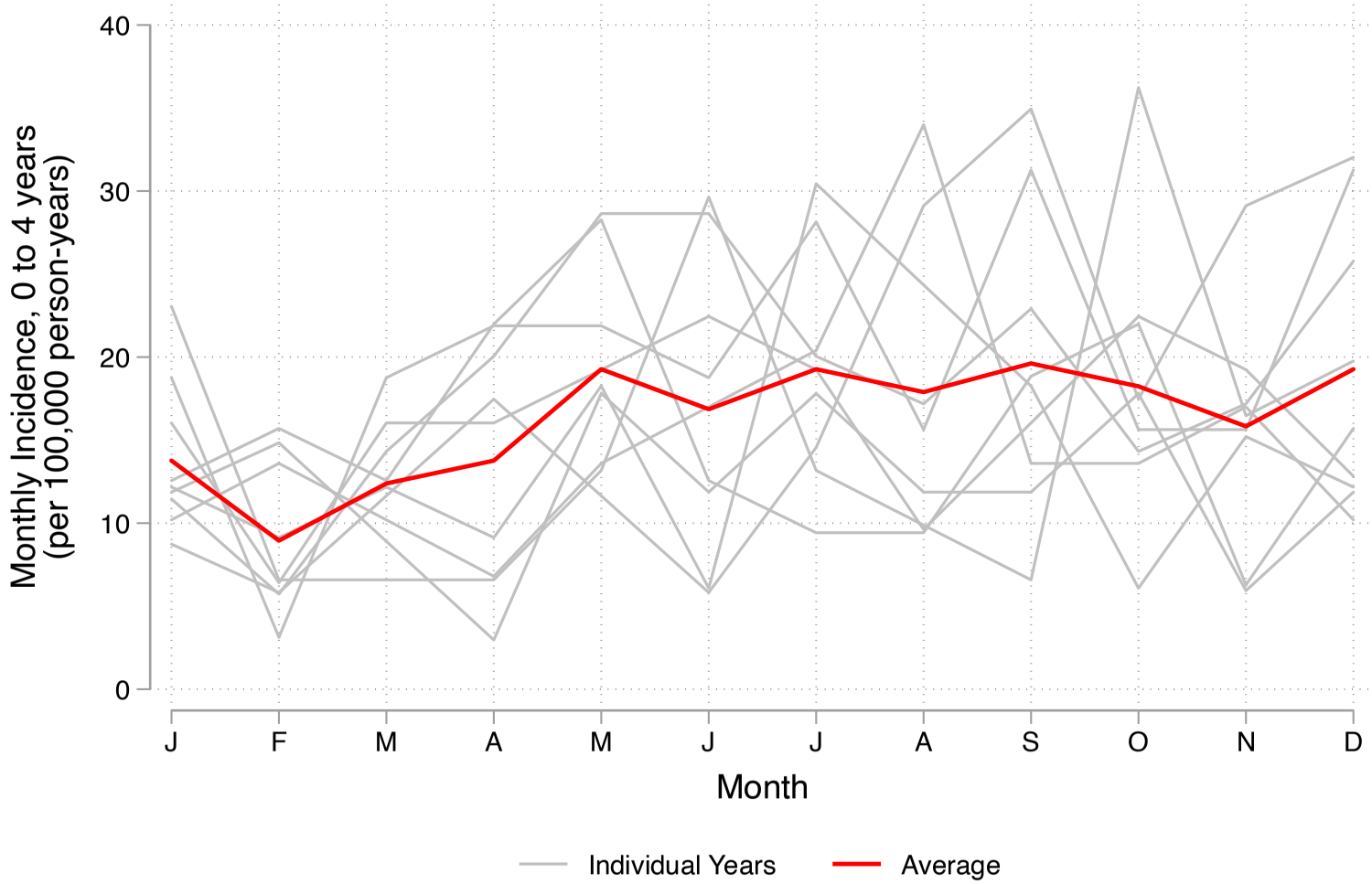
Data from the Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Figure 4.S2d: Monthly Variation of Kawasaki Disease Treatment Rates in Australia, by Region: 2007–2015, South Australia



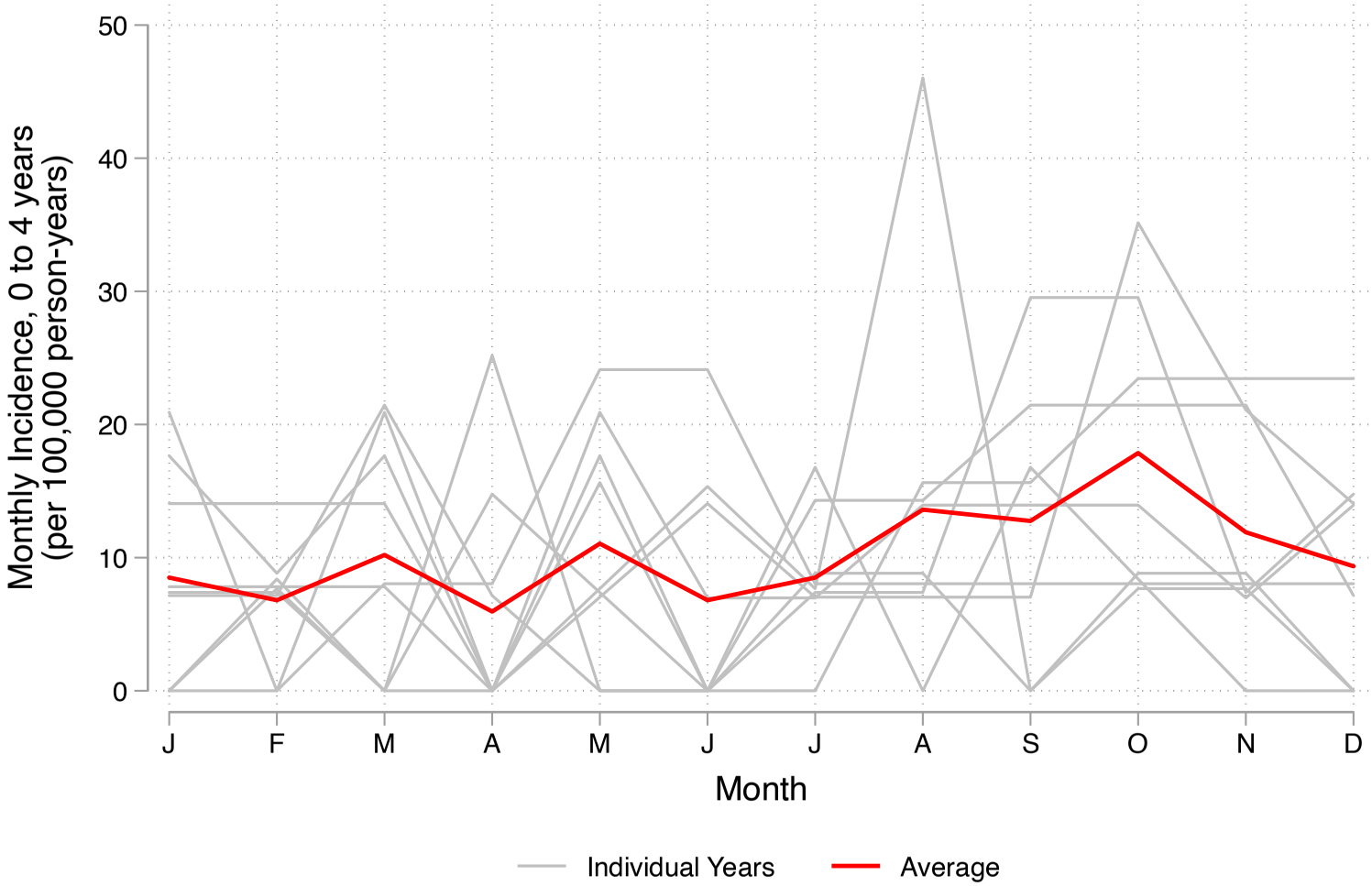
Data from the Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Figure 4.S2e: Monthly Variation of Kawasaki Disease Treatment Rates in Australia, by Region: 2007–2015, Victoria and Tasmania



Data from the Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Figure 4.S2f: Monthly Variation of Kawasaki Disease Treatment Rates in Australia, by Region: 2007–2015, Western Australia



Data from the Supply Tracking and Reporting System–Australian Red Cross Lifeblood.

Chapter 5

The following manuscript, entitled "Live vaccines following intravenous immunoglobulin for Kawasaki disease: Are we vaccinating appropriately?" was published in *The Journal of Paediatrics and Child Health* in 2023. The goal of the study was to determine whether Australian children who had received IVIG for KD are potentially at risk for vaccine preventable illnesses due to IVIG's interference with live vaccines. Australian guidelines recommend that live vaccines be postponed for at least 11 months after IVIG for KD, yet this study found that most children who received IVIG less than 11 months prior to a scheduled live vaccine did not have that vaccination appropriately postponed.

The evidence for the 11-month postponement recommendation was reviewed and found to be of poor quality. In the absence of high-quality evidence to guide immunisation guidelines we proposed that further research was needed and recommended that practitioners remain vigilant as to IVIG's interference with live vaccines.

The authors reported no conflicts of interest. Ethical approval was granted by the Human Research Ethics Council of the Sydney Children's Hospitals Network. Approval 2021/ETH11191 with site specific approval 2021/STE03255 and 2021/STE03256.

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ORIGINAL ARTICLE

Live vaccines following intravenous immunoglobulin for Kawasaki disease: Are we vaccinating appropriately?

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Aim: Australian and New Zealand guidelines recommend that live vaccines be postponed for 11 months after treatment of Kawasaki disease (KD) with intravenous immunoglobulin (IVIG). We aimed to describe patterns of live-vaccine administration after KD treatment, focusing on the measles–mumps–rubella/measles–mumps–rubella–varicella (MMR/MMRV) vaccines, and to compare real-world practice with current recommendations.

Methods: We combined data from inpatient Electronic Health Records and the Australian Immunisation Register for all children who received IVIG for the treatment of KD under the age of 5 years at two Australian tertiary children's hospitals over a 12-year period. Children who received IVIG <11 months before a scheduled MMR/MMRV were deemed 'at risk' of breaching the guidelines, and those whose subsequent vaccination occurred <11 months after the IVIG were deemed to have 'breached' the guidelines.

Results: Of those at risk, three-quarters (76%) breached the guidelines for their first MMR/MMRV. Findings were similar (50%–80%) for the second MMR/MMRV dose.

Conclusions: The majority of Australian children treated for KD with IVIG may not be optimally protected by MMRV vaccination. Immunisation systems should address this avoidable risk.

Key words: immunisation; intravenous immunoglobulin; Kawasaki disease.

What is already known on this topic

1 The incidence of Kawasaki disease (KD) in Australia is increasing.
2 Australian guidelines recommend postponing live attenuated viral vaccines – principally measles–mumps–rubella (MMR) and measles–mumps–rubella–varicella (MMRV) – for 11 months following intravenous immunoglobulin (IVIG) for KD, due to risk of interference with seroconversion.
3 One Dutch study reported that clinicians did not routinely adhere to the guidelines recommending postponement of MMR/MMRV vaccinations following IVIG for KD.

What this paper adds

1 Almost 40% of children under 5 years of age who received IVIG for KD were at risk of breaching Australian guidelines that recommend postponing MMR/MMRV vaccines for at least 11 months following IVIG.
2 We identify in our 'at risk' cohort, between 50% and 80% of children did not have their MMR/MMRV vaccine postponed and have been potentially sub-optimally immunised and protected.
3 We review the evidence base for current Australian immunisation guidelines recommending postponement of MMR/MMRV vaccines following IVIG for KD.

Kawasaki disease (KD) is a systemic vasculitis that typically affects children under the age of 5 years.[1] It causes inflammation of medium-sized arteries and can lead to aneurysm formation, particularly of the coronary arteries. Intravenous immunoglobulin (IVIG) reduces the incidence of coronary artery aneurysm and Australian and international clinical practice guidelines recommend that children with KD receive 2 g/kg IVIG as primary therapy.[1–3]

IVIG is a therapeutic product derived from the pooled plasma of thousands of human donors.[4] It contains polyclonal antibodies (mostly IgG) and was initially used to treat disorders of humoral immunity such as agammaglobulinaemia.[4] Subsequent clinical experience with IVIG led to an appreciation of its immunomodulatory effects,[5] and IVIG is now approved for use in a wide range of clinical conditions.[6]

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Passively acquired polyclonal antibodies (such as from IVIG) can interfere with seroconversion following immunisation with live attenuated viral vaccines.[7,8] Measles-containing vaccines (measles–mumps–rubella, MMR; measles–mumps–rubella–varicella, MMRV; henceforth we use 'MMR/MMRV' to refer to both vaccines) are live-attenuated viral vaccines that are typically administered in the first few years of life.

It is generally agreed that children who receive IVIG for KD prior to receiving an MMR/MMRV should have vaccination postponed; however, there is no international consensus regarding the period of postponement. Guidelines in Australia[9] and New Zealand[10] align with those from North America, recommending that live vaccines be postponed for 11 months after receiving IVIG. Canadian and American guidelines,[1,11,12] all cite recommendations from the Advisory Committee on Immunization Practices,[13] which advises American states and agencies on matters relating to immunisation.

The 11-month interval was derived by extrapolating from an estimated immunoglobulin half-life of 30 days to a theoretical physiological persistence for 10 months, with a 1-month 'grace period'.[13] The recommendation has remained unchanged since 1994, and cites a limited body of literature.[14] That literature consists of two studies: the first (described in two conference abstracts[15,16]) studied the persistence of passively acquired measles antibodies following IVIG in 44 children with KD. Measles antibodies persisted for between 3 and 12 months; all children subsequently immunised had an adequate response; however, the timing of the immunisation was not specified.[16] The second was a small ($n = 167$) randomised controlled trial of intramuscular immunoglobulin for the prevention of invasive bacterial disease (*Haemophilus influenza* type B and *Streptococcus pneumoniae*) among Apache children, in which it was observed that seroconversion to measles immunisation was inhibited up to 5 months after a series of intramuscular injections of immunoglobulin at 80 mg/kg.[17]

Japanese guidelines recommend an interval between IVIG and live vaccine administration of 6–7 months,[18] based on a cohort study of the persistence of passively acquired measles antibodies following IVIG showing measles antibodies were undetectable in 89% of patients 6 months after IVIG.[19] Recent European recommendations for the treatment of KD state live vaccines 'should' be deferred for 6 months, but equivocate – suggesting that the MMR and MMRV 'might' be deferred for 'at least 11 months', while also asserting that children at high risk of exposure to measles should be vaccinated earlier.[2]

More rigorous studies have been published since those summarised above. Tacke *et al*. retrospectively evaluated seroconversion to MMR at different intervals following IVIG.[20] They found the rates of seroconversion to the mumps and rubella components (but not the measles component) did not differ between cases and controls ($n = 198$) for those immunised 6–9 months after IVIG, and that seroconversion to all components was equivalent for those immunised more than 9 months after IVIG.[20] Without more data on the interval to immunisation beyond 9 months it cannot be determined at what interval measles seroconversion was assured. In an uncontrolled study, Morikawa *et al*. prospectively evaluated seroconversion to MMRV given 6 months after IVIG at 2 g/kg.[21] They found poor rates of seroconversion (especially for mumps and varicella), noting that a booster dose at 12 months post-IVIG was effective. Those authors subsequently assessed seroconversion to MMRV given 6 and 9 months after two doses of IVIG (i.e. 4 g/kg).[8] They found universal seroconversion to the measles and rubella components when given 9 months post-IVIG, but again observed strikingly low rates of seroconversion to the mumps and varicella components. This contrasts with previous studies in which measles seroconversion was most affected by IVIG.[20] Without a control arm it is unclear whether confounding factors account for the poor response to mumps and varicella.

There is evidence of variation in real-world practice. In a study by Tacke *et al*. from the Netherlands it was observed that 78% of children who received IVIG did not have their scheduled MMRV vaccine appropriately delayed by the local recommendation of 6 months.[20]

We aimed to describe patterns of immunisation in children treated with IVIG for KD at two tertiary Australian children's hospitals to determine current adherence with Australian guidelines and identify targets for improvement.

Materials and Methods

We undertook a retrospective audit of MMR/MMRV administration of children who received IVIG for KD before the age of 5 years at two tertiary children's hospitals in Sydney, Australia over a 12-year period. Inpatient datasets were queried for all admissions with any discharge diagnosis of KD (ICD-10-AM codes M30.3, G635 and I245) between 1 November 2007 and 1 November 2019, limited to children aged less than 5 years at discharge. The Electronic Health Record was reviewed to confirm receipt of IVIG and document the date of administration. The Australian Immunisation Register (AIR)[22] was accessed to determine the date of MMR/MMRV administration. Inclusion and exclusion criteria are shown in Figure 1.

The Australian National Immunisation Program (NIP) Schedule previously recommended the first MMR/MMRV ('MMR1') be given at 12 months of age and the second ('MMR2') at 4 years of age (the 'previous schedule').[23] In response to suboptimal measles susceptibility among infants, and to bring Australian practice in line with other countries (especially in Europe), the recommended timing for the MMR2 was brought forward to 18 months of age from July 2013 ('current schedule').[9,24] We defined three groups of children who received IVIG <11 months before an MMR/MMRV was scheduled to be given, who we defined as being 'at risk' of breaching the guidelines:

1 For all children: those who received IVIG between 1 and 12 months of age (i.e. <11 months before MMR1 was due).
2 For children aged 18 months before 1 July 2013: those who received IVIG between 37 and 48 months of age (i.e. <11 months before MMR2 was due under the previous schedule).
3 For children aged 18 months after 1 July 2013: those who received IVIG between 7 and 18 months of age (i.e. <11 months before MMR2 was due under the current schedule).

For each group, we calculated the proportion who then received the MMR less than 11 months after the dose of IVIG (i.e. the

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proportion of those 'at risk' for breaching the guidelines that subsequently 'breached' the guidelines).

If children received more than one dose of IVIG, we categorised the dose as follows:

- IVIG given <30 days after a previous dose of IVIG was considered retreatment within a single episode of KD.
- IVIG given ≥30 days after a previous dose of IVIG was considered treatment of a new (i.e. recurrent) episode of KD.[25]

For episodes of KD requiring multiple doses of IVIG, we used the date of the last dose of IVIG for the analysis. For children with multiple episodes of KD, we considered all episodes for analysis as separate IVIG exposures.

Descriptive demographic data were summarised based on the age of each child at presentation of their first episode of KD. Analysis was performed using Stata/BE 17.0 for Mac (StataCorp, College Station, TX, USA).

Ethics approval was granted by the Sydney Children's Hospital Network Human Research and Ethics Committee. For children identified to have received a measles-containing vaccine less than 11 months after IVIG, we undertook to inform both their families and general practitioners so that additional booster doses could be offered.

Results

There were 567 inpatient encounters with a discharge diagnosis code of KD. Of those, 417 were admissions for the treatment of an acute episode of KD; the remainder largely constituted diagnostic day admissions for echocardiography and did not receive IVIG during that admission; these encounters were excluded. Two children were excluded as the diagnosis of KD had been subsequently revised. The 417 admissions for acute KD represented 396 discrete episodes of KD occurring in 389 individuals (Fig. 1). Ninety-four (24.2%) children required more than one dose of IVIG within an admission for acute KD (i.e. they required re-treatment). Twenty-one children (5.4%) were readmitted to hospital after initial discharge during a single episode of KD, presumably for a recurrence of symptoms, and required retreatment with IVIG. Seven children (1.8%) had recurrence of KD during the study period.

Basic demographic data are shown in Table 1. Over 95% of all children included in the analysis received either MMR or MMRV vaccine (Table S1, Supporting Information).

Overall, of the children under the current vaccination schedule, 39.5% (86/218) were at risk of breaching the recommendations for either vaccine; 64% (55/86) of those at risk breached the recommendations for at least one vaccine dose (Table 2). Under the previous schedule, 28.7% (49/171) of children were at risk of breaching either vaccine and this was proportionately fewer than the current schedule ($P = 0.026$, Table S2, Supporting Information).

Overall, regarding the MMR1, 23.1% (90/389) of children received IVIG for KD <11 months before that vaccine was due (i.e. were at risk of breaching the recommendations); of those, 76% (68/90) went on to receive the MMR1 vaccine <11 months after receiving IVIG (i.e. breached the recommendations, Table 3, Fig. 2). Regarding MMR2, 11.7% (20/171) of children under the previous schedule were at risk for that vaccine, of whom 80% (16/20) breached. Of those under the current schedule, 27.5% (60/218) were at risk, of whom 50% (30/60) breached (Table 3, Fig. 3).

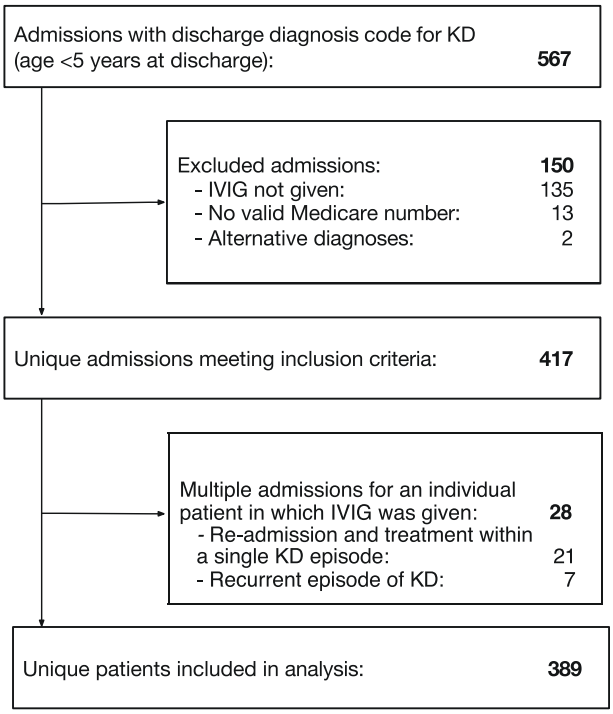

Fig. 1 Study flowchart. IVIG given <30 days after a previous dose of IVIG was considered retreatment within a single episode of KD. IVIG given ≥30 days after a previous dose of IVIG was considered treatment of a new (i.e. recurrent) episode of KD. IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Table 1 Demographic and patient characteristics

	Total ($n = 389$)
Male, *n* (%)	240 (61.7)
Retreatment within episode, *n* (%)	94 (24.2)
Recurrent episode, *n* (%)	7 (1.8)
Age at first IVIG (months), median (IQR)	25 (13–41)
Age at first IVIG (months), *n* (%)	
<6 months	36 (9.3)
6–<12 months	55 (14.1)
12–<18 months	45 (11.6)
18–<24 months	49 (12.6)
24–<36 months	79 (20.3)
36–<48 months	61 (15.7)
≥48 months	64 (16.5)

Descriptive data of patient cohort at the time of the first episode of Kawasaki disease. IVIG given <30 days after a previous dose of IVIG was considered retreatment within a single episode of KD. IVIG given ≥30 days after a previous dose of IVIG was considered treatment of a new (i.e. recurrent) episode of KD. IQR, interquartile range; IVIG, intravenous immunoglobulin.

Table 2 Risk of breaching recommendations regarding measles-containing vaccines after intravenous immunoglobulin therapy for Kawasaki disease: MMR1 or MMR2 under the current schedule

	At risk		
	No	Yes	Total
Breached			
No, *n* (%)	128 (97.0)	31 (36.0)	159 (72.9)
Yes, *n* (%)	4 (3.0)	55 (63.9)	59 (27.1)
Total	132	86	218

Timing of measles-containing vaccines after receiving intravenous immunoglobulin (IVIG) for Kawasaki disease (KD). The *Australian Immunisation Handbook* recommends postponing live vaccines for 11 months after IVIG for KD. 'At risk' means that a child received IVIG for the treatment of KD less than 11 months prior to a scheduled measles-containing vaccine. 'Breached' means that a measles-containing vaccine was given less than 11 months after a child received IVIG for the treatment of KD. MMR1 refers to the first measles-containing vaccine on the National Immunisation Programme Schedule and is recommended to be given at 12 months of age. MMR2 refers to the second measles-containing vaccine, which is recommended to be given at 18 months of age. Children who were older than 18 months of age on 1 July 2013 were immunised according to the previous schedule (not included here). MMR, measles–mumps–rubella.

Table 3 Adherence with recommendations regarding measles-containing vaccines after intravenous immunoglobulin therapy for Kawasaki disease

		At risk		
		No	Yes	Total
MMR1 (all)	Breached			
	No, *n* (%)	293 (98.0)	22 (24.4)	315 (81.0)
	Yes, *n* (%)	6 (2.0)	68 (75.6)	74 (19.0)
	Total, *n* (%)	299 (100.0)	90 (100.0)	389 (100.0)
		At risk		
		No	Yes	Total
MMR2 (previous schedule)	Breached			
	No, *n* (%)	146 (96.7)	4 (20.0)	150 (87.7)
	Yes, *n* (%)	5 (3.3)	16 (80.0)	21 (12.3)
	Total, *n* (%)	151 (100.0)	20 (100.0)	171 (100.0)
		At risk		
		No	Yes	Total
MMR2 (current schedule)	Breached			
	No, *n* (%)	154 (97.5)	30 (50.0)	184 (84.4)
	Yes, *n* (%)	4 (2.5)	30 (50.0)	34 (15.6)
	Total, *n* (%)	158 (100.0)	60 (100.0)	218 (100.0)

Timing of measles-containing vaccines after receiving intravenous immunoglobulin (IVIG) for Kawasaki disease (KD). The *Australian Immunisation Handbook* recommends postponing live vaccines for 11 months after IVIG for KD. 'At risk' means that a child received IVIG for the treatment of KD less than 11 months prior to a scheduled measles-containing vaccine. 'Breached' means that a measles-containing vaccine was given less than 11 months after a child received IVIG for the treatment of KD. MMR1 refers to the first measles-containing vaccine on the National Immunisation Programme (NIP) Schedule. MMR2 refers to the second measles-containing vaccine on the NIP Schedule. MMR1 is scheduled to be given at 12 months of age. The schedule changed on 1 July 2013 with regards to MMR2: under the previous schedule MMR2 was given at 4 years of age; under the current schedule MMR2 is given at 18 months of age. Children who were less than 18 months of age on 1 July 2013 were immunised according to the current schedule. MMR, measles–mumps–rubella.

Discussion

We analysed MMR/MMRV administration data over a 12-year period for children who received IVIG for KD before 5 years of age. A recent study confirmed that the incidence of KD in Australia is increasing, with the hospitalisation rate among children under 5 estimated to be 17.51 per 100 000 annually (95% CI 16.59–18.47) between 2013 and 2017.[25] This figure represents an average of 272 episodes of KD per year among children under 5 years in Australia (see supplementary table 1 of reference 17). We found that since the current measles vaccination schedule was commenced, 40% of children under 5 years of age who received IVIG for KD were at risk of breaching these recommendations, which suggests that over 100 children may be at risk of breaching national recommendations for live vaccines after IVIG each year in Australia. Furthermore, this number is expected to rise in line with population growth and increasing incidence of KD and the use of IVIG.

A major strength of our study was a relatively large cohort size, which included children admitted at two hospitals over 12 years. There were also important limitations. As we were unable to undertake comprehensive case reviews for each child included in the analysis, we relied on discharge diagnosis codes, which could not be validated against clinical data to identify children diagnosed with KD. Notwithstanding, the aim of the study was to understand the subsequent vaccination patters of children who received IVIG for KD, rather than KD diagnosis *per se*. A further limitation was our reliance on the AIR for the vaccination history. Only children with a valid Medicare number (either Australian citizens or those on a permanent residency visa) have vaccination details entered into the AIR; we were therefore unable to consider vaccination patterns for children in other circumstances, who may be at a higher risk for breaching immunisation recommendations. Finally, we did not seek to understand the drivers of deviations in practice, which is the critical next step in seeking to improve the quality of care being delivered.

The recent global resurgence of measles – particularly in South-East Asia and the Pacific – has highlighted the critical importance of effective immunisation in achieving measles eradication.[26] One potential means of improving the post-IVIG measles vaccination guideline adherence in patients with KD would

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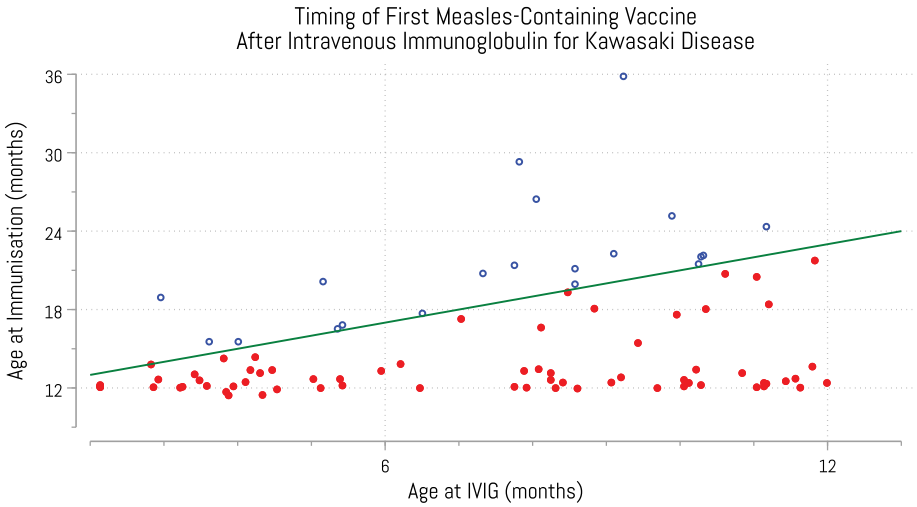

Fig. 2 MMR1 following intravenous immunoglobulin (IVIG) for Kawasaki disease. Comparison to the *Australian Immunisation Handbook* guidelines for live vaccines after IVIG. Children given IVIG <11 months before a scheduled MMR/MMRV were deemed 'at risk' of breaching the guidelines, and those whose subsequent vaccination occurred <11 months after the IVIG were deemed to have 'breached' the guidelines. All children who were at risk are depicted, with those who breached coloured red. Time from IVIG to immunisation: (o), >11 months; (●), <11 months; (——), IVIG + 11 months. MMR/MMRV, measles–mumps–rubella/measles–mumps–rubella–varicella.

be through improved health-care professional and family education. Another would involve linking the electronic clinical database which in Australia records vaccination status (AIR) and the administrative database which records IVIG utilisation for KD (Bloodstar) which would allow systematic flagging of 'at risk' children, so immediate identification of patients who required a delay in measles vaccination at the point of care rather than retrospectively as we have done in this study. At present, this is not possible as the databases mentioned are maintained by separate Government departments; AIR by the Australian Department of Health and Aged Care and Bloodstar by the National Blood Authority.

The recommendations for vaccination deferment post-IVIG infusion for KD we have evaluated in our study have remained unchanged for many years and are based on small historical studies. There is clearly a need for better contemporary data to allow the development of better-informed recommendations.

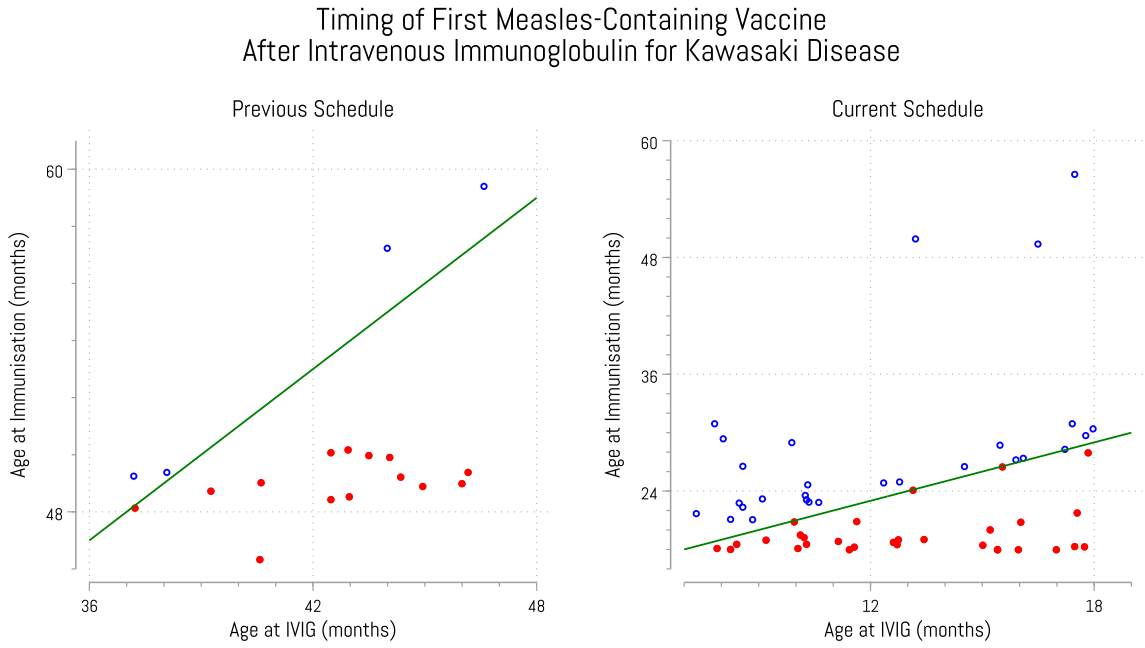

Fig. 3 MMR2 following intravenous immunoglobulin (IVIG) for Kawasaki disease. Comparison to the *Australian Immunisation Handbook* guidelines for live vaccines after IVIG. Children given IVIG <11 months before a scheduled MMR/MMRV were deemed 'at risk' of breaching the guidelines, and those whose subsequent vaccination occurred <11 months after the IVIG were deemed to have 'breached' the guidelines. All children who were at risk are depicted, with those who breached coloured red. The Australian National Immunisation Program Schedule previously recommended that the first MMR/MMRV ('MMR1') be given at 12 months of age and the second ('MMR2') at 4 years of age (the previous schedule).[15] A change to the schedule, which took effect from July 2013, saw the second dose brought forward to 18 months of age (the current schedule). Time from IVIG to immunisation: (o), >11 months; (●), <11 months; (——), IVIG + 11 months. MMR/MMRV, measles–mumps–rubella/measles–mumps–rubella–varicella.

Conclusions

Our findings suggest there is a cohort of Australian children for whom IVIG treatment of KD may have put them at risk of vaccine-preventable infections following immunisation with live vaccines that occurred outside the recommended post-IVIG schedule. Given the poor quality of the data that has informed those recommendations, we need to better understand the magnitude and duration of interference by IVIG with protection from live vaccines. In the interim, managing children with KD should be aware that IVIG may interfere with responses to live vaccines and ensure adherence with national guidelines regarding postponement of live vaccines for 11 months post-IVIG. This important information should be communicated to patient's families and primary care providers as part of standard management of children with KD.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Overall measles-containing vaccine coverage among those given intravenous immunoglobulin for Kawasaki disease.
Table S2. Risk of breaching recommendations regarding measles-containing vaccines after intravenous immunoglobulin therapy for Kawasaki disease: MMR1 or MMR2 under the old schedule.

Live vaccines following intravenous immunoglobulin for Kawasaki disease: Are we vaccinating appropriately?

Supplementary Results

Table 5.S1: Overall Measles-Containing Vaccine Coverage Among Those Given Intravenous Immunoglobulin for Kawasaki Disease

	MMR1 (All Patients)	MMR2 (Previous Schedule)	MMR2 (Current Schedule)
Received vaccine			
Yes, n (%)	380 (97.7)	165 (96.5)	210 (96.3)
No, n (%)	9 (2.3)	6 (3.5)	8 (3.7)
Total	**389**	**171**	**218**

MMR, measles-mumps-rubella. MMR1 refers to the first measles-containing vaccine on the National Immunisation Programme (NIP) Schedule. MMR2 refers to the second measles-containing vaccine on the NIP Schedule; under the Current Schedule MMR2 also contains varicella. MMR1 is scheduled to be given at 12 months of age. The schedule changed on 1st July 2013 with regards to MMR2: under the previous schedule MMR2 was given at 4 years of age; under the current schedule MMR2 is given at 18 months of age. Children who were less than 18 months of age on 1st July 2013 were immunised according to the current schedule.

Table 5.S2: Risk of Breaching Recommendations Regarding Measles-Containing Vaccines after Intravenous Immunoglobulin Therapy for Kawasaki Disease: MMR1 or MMR2 Under the Old Schedule

	At Risk		
	No	**Yes**	**Total**
Breached			
No, n (%)	100 (82.0)	14 (28.6)	114 (66.7)
Yes, n (%)	22 (18.0)	35 (71.4)	57 (33.3)
Total	**122**	**49**	**171**

Timing of measles-containing vaccines after receiving intravenous immunoglobulin (IVIG) for Kawasaki disease (KD). The *Australian Immunisation Handbook* recommends postponing live vaccines for 11 months after IVIG for KD. "At Risk" means that a child received IVIG for the treatment of KD less than 11 months prior to a scheduled measles-containing vaccine. "Breached" means that a measles-containing vaccine was given less than 11 months after a child received IVIG for the treatment of KD.

MMR, measles-mumps-rubella. MMR1 refers to the first measles-containing vaccine on the National Immunisation Programme (NIP) Schedule and is recommended to be given at 12 months of age. MMR2 refers to the second measles-containing vaccine, which was recommended to be given at 4 years of age. Children who were less than 18 months of age on 1st July 2013 were immunised according to the current schedule (not included here).

Chapter 6

The following manuscript, entitled "Prospective Surveillance of Kawasaki Disease in Australia: 2019–21" has been prepared for submission to *The Lancet Regional Health—Western Pacific* for consideration for publication. It presents the findings of a cohort of patients prospectively enrolled in the course of a multicentre surveillance programme at sites across Australia. That programme, coordinated and administered by the Paediatric Active Enhanced Disease Surveillance (PAEDS) network, is the largest of its kind from the Southern Hemisphere. The manuscript that follows includes data for children recruited between January 1st 2019 and December 31st 2021; enrolment continues, with 765 cases at the time of writing.*

The study sought to describe the clinical presentation, management, and outcomes of children diagnosed with KD in Australia. All children with clinician-diagnosed KD were enrolled, providing important insights into the diagnostic practices of Australian clinicians. One of the key findings of this study was that a significant proportion of those diagnosed with KD did not fulfil the diagnostic criteria outlined in the 2017 statement by the American Heart Association. The Australian approach to the use of aspirin was also described.

The authors reported no conflicts of interest. Ethical approval for the PAEDS network (including the KD study) was granted by the Human Research Ethics Committee of the Sydney Children's Hospitals Network (HREC/18/SCHN/72).

* Late March, 2023.

Prospective Surveillance of Kawasaki Disease in Australia: 2019–21

Abstract

Aim: Kawasaki disease (KD) is frequently encountered by Australian paediatricians. We sought to describe clinical practice with regards to diagnosis and management, and to examine disease outcomes both during the acute hospital admission and at medium-term follow-up.

Methods: This study was conducted at eight tertiary paediatric hospitals across Australia as part of an established surveillance network—Paediatric Active Enhanced Disease Surveillance (PAEDS). Children under the age of 16 years who were treated for KD were enrolled in a prospective cohort study. Comprehensive clinical data, including reports of echocardiograms performed during the admission and at 6–8 weeks follow-up, were collected. Cases were classified as Complete KD, Incomplete KD, or Uncertain KD based on the 2017 American Heart Association (AHA) diagnostic criteria.

Results: We identified 483 children with a clinical diagnosis of KD: 54.7% were classified as Complete KD, 8.9% as Incomplete KD, and 36.4% as Uncertain KD. Most children (86.9%) treated with aspirin only received low-dose aspirin (3–5 mg/kg/day), as recommended in Australian guidelines. Over 99% received intravenous immunoglobulin (IVIG); of those, 29.0% received additional doses of IVIG due to perceived treatment non-response. There was marked variability in how treatment non-response was diagnosed.

Conclusions: A significant proportion of children treated for KD did not fulfil the AHA diagnostic criteria. The rate of retreatment with IVIG was high, which may reflect overdiagnosis of treatment failure in the absence of an agreed definition. International collaboration is needed to better define IVIG non-responsiveness in the treatment of KD and to better understand the underlying mechanisms of this phenomenon.

Introduction

Kawasaki disease (KD) is a systemic vasculitis that predominantly affects children under 5 years of age.[1] It causes inflammation of medium-sized arteries, and can lead to aneurysm and stenosis of the coronary arteries. In the absence of a gold-standard test the diagnosis remains clinical, requiring the observation of a minimum set of cardinal clinical signs.[2] Multiple diagnostic criteria have been proposed and revised, reflecting the evolving understanding of the condition's clinical presentation.[1–3] The American Heart Association (AHA) updated their recommendations for the diagnosis of KD in 2017,[1] allowing for experienced clinicians to diagnose complete KD before day 5 of fever and providing an algorithm for diagnosing incomplete KD.

The management of KD relies on intravenous immunoglobulin (IVIG) as the only intervention proven to reduce the incidence of aneurysms;[4] international guidelines agree that children with KD should receive 2 g/kg of IVIG as a single dose.[1–3] Guidelines also recommend the use of aspirin, however there is a lack of consensus around dose: most recommend that children be commenced on moderate-dose (30–50 mg/kg/day) or high-dose (80–100 mg/kg/day) aspirin, before stepping down to low-dose (3–5 mg/kg/day) aspirin for thromboprophylaxis.[1–3] Recommendations on other aspects of the management of KD—such as the diagnosis and management of cases that fail to respond to initial IVIG—has far less consensus.[5]

We undertook a multicentre prospective cohort study of KD in Australia to describe the clinical presentation and disease course of KD in Australia and understand the diagnostic and therapeutic decisions of Australian clinicians.

Methods

Active sentinel surveillance for KD was conducted through the Paediatric Active Enhanced Disease Surveillance (PAEDS) network (https://www.paeds.org.au).[6] The PAEDS network is a hospital-based active surveillance system in Australia that prospectively identifies admitted cases of selected serious childhood conditions for clinical research.[7,8] Surveillance commenced from January 1, 2019 at seven major Australian hospitals[*] (including six of Australia's eight specialist paediatric hospitals) with an eighth site[†] (a specialist paediatric hospital) contributing data from January 1,

[*] The Children's Hospital at Westmead (CHW; New South Wales), Royal Children's Hospital (RCH; Victoria), Monash Health (MH; Victoria), Women's and Children's Hospital (WCH; South Australia), Perth Children's Hospital (PCH, Western Australia), Royal Darwin Hospital (RDH, Northern Territory), and Queensland Children's Hospital (QCH; Queensland)

[†] Sydney Children's Hospital (SCH, New South Wales)

2020 (see Supplementary Methods). We present data for the cohort to December 31, 2021.

All children aged <16 years admitted to a participating hospital with a diagnosis of acute KD during the study period were eligible for inclusion. Children were excluded from the study if the diagnosis of KD was subsequently overturned. Where the diagnosis of KD was unclear the decisions of treating clinicians were used to determine the level of diagnostic certainty: children given IVIG or aspirin for presumed KD were included (at least until the diagnosis was overturned). Emergency department and inpatient databases were screened daily by dedicated surveillance staff to identify potential KD cases. Hospital records were periodically audited for individuals with a discharge diagnosis of KD (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification code M30.3). Where cases had not been prospectively identified the inpatient records were retrospectively assessed for inclusion.

Of particular note was the emergence of a new systemic inflammatory condition of childhood during this study – namely Paediatric Inflammatory Multisystem Syndrome – Temporally associated with SARS-CoV-2 (PIMS-TS), also known as the Multisystem Inflammatory Syndrome in Children associated with COVID-19 (MIS-C). PIMS-TS was first reported from the United Kingdom in early 2020 in the context of the global COVID-19 pandemic.[9] In response the Australian Government funded a prospective surveillance program for PIMS-TS in Australia. PIMS-TS surveillance was undertaken by the same research network that was conducting the KD surveillance described here, using a modified version of the Case Reporting Form used for this study. Children were categorised as 'Confirmed PIMS-TS'[*] or 'Possible PIMS-TS' and could be concurrently included KD surveillance. Children who were categorised as 'Confirmed PIMS-TS' were subsequently excluded from KD surveillance, whereas those categorised as 'Possible PIMS-TS' were not excluded.

[*] The case definition for PIMS-TS used in that study was as follows:[10]
Children and adolescents (up to 18 years of age) with fever ≥3 days AND two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); age-specific hypotension or "shock" within first 24 hours of presentation; features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated d-Dimers); acute gastrointestinal problems (diarrhoea, vomiting or abdominal pain). ALL of the following were also required: elevated markers of inflammation such as ESR, C-reactive protein or procalcitonin; exclusion of other infectious causes of inflammation, including bacterial sepsis, staphylococcal or streptococcal toxic shock syndromes; and, evidence of SARS-CoV-2 infection (positive RT-PCR), or confirmed contact with a person with SARS-CoV-2 infection (public health defined), or confirmed positive SARS-CoV-2 serology).

Study data were collected and managed using the REDCap electronic data capture tool hosted at The University of Sydney. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.[11,12] Participant data was able to be edited only by research staff at each site, and designated investigators centrally.

Demographic, clinical and follow-up data were collected from the medical records. Information on recent vaccine administration was sought from caregivers and confirmed via the Australian Immunisation Registry.[13] Reports of inpatient echocardiograms, as well as echocardiograms at 6–8 weeks follow-up, were analysed. Maximum coronary artery dimensions were used to generate Z-scores using the method of Dallaire & Dahdah;[14] where this was not possible, but a Z-score had been documented, the documented Z-score was used.

The AHA diagnostic criteria were applied retrospectively. Briefly, children were classified as having complete KD or incomplete KD, according to the 2017 AHA Guideline[1]; those not fulfilling the criteria for either diagnosis were classified as uncertain KD. Non-response to primary therapy was determined by the decision of the treating clinicians to administer a second dose of IVIG or treatment escalation (such as corticosteroids) within a single episode of KD due to persistence or recrudescence of fever, clinical signs, or raised inflammatory markers after an initial dose of IVIG. Statistical analysis was performed using Stata/IC 17.0 for Mac (StataCorp 2017. Stata Statistical Software: Release 17. College Station, Texas.

Ethical approval was granted by the Human Research Ethics Committee of the Sydney Children's Hospitals Network (HREC/18/SCHN/72). The study operated under a waiver of consent to allow the collection of de-identified patient data however families could elect to be removed from the study at their discretion.

Results

We identified 493 children with an initial diagnosis of KD. Ten patients were excluded: nine had their KD diagnosis subsequently revised while one family asked not to be included in the study (**Figure 6.1**). Thus, 483 cases were included in the analysis: 54.7% (264/483) were classified as complete KD, 8.9% (43/483) as incomplete KD, and 36.4% (176/483) as uncertain KD (**Table 6.1**). The AHA criteria allow for the diagnosis of complete KD to be made by an

experienced clinician after as little as 3 days of fever—under those criteria 62 of the uncertain KD cases were reclassified as complete KD, with 114 (23.6%) still uncertain. (**Figure 6.2**).

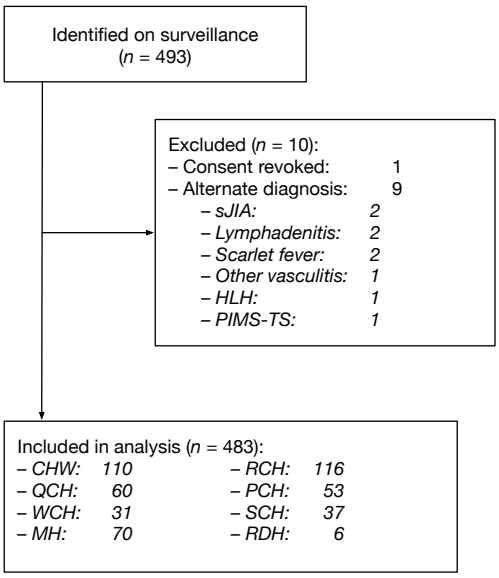


Figure 6.1:
Flowchart of Study Inclusion and Exclusion Numbers

HLH, hemophagocytic lymphohistiocytosis; PIMS-TS, paediatric inflammatory multisystem syndrome—temporally associated with SARS-CoV infection; sJIA, systemic onset juvenile idiopathic arthritis. Site abbreviations as previously described.

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the cohort are shown in **Table 6.1**. The median age at admission was 2.8 years (IQR 1.3–4.6); those with incomplete KD were significantly younger on average than those with complete or uncertain KD (median 1.5 years, IQR 0.4–3.5 years; $p = 0.002$). The male to female ratio was 1.46:1 and did not differ between diagnostic groups. The most frequent country of birth of patients and their parents was Australia, followed by China and India (**Supplementary Table 6.1**). The most common cardinal clinical criterion overall (not including fever) was rash (88.6%, 428/483), followed by conjunctival injection (85.9%, 415/483); rash was the second most frequent cardinal clinical criterion among those with incomplete KD, after conjunctival injection.

Pre-treatment laboratory finding are shown in **Table 6.1** and **Figure 6.3**. Anaemia was common: 55.0% (262/476) of age-normalised haemoglobin results were more than two standard deviations below the mean. Leukocytosis $\geq 15 \times 10^9$/L was observed in 43.8% (210/480), most frequently with a neutrophil predominance (>50% neutrophils in 83.8%, 397/474). No laboratory findings differed significantly between those with Complete KD and those with Uncertain KD. COVID testing (which started in 2020) occurred in 46.2% of cases (271/483), with only 2 cases returning a positive result.

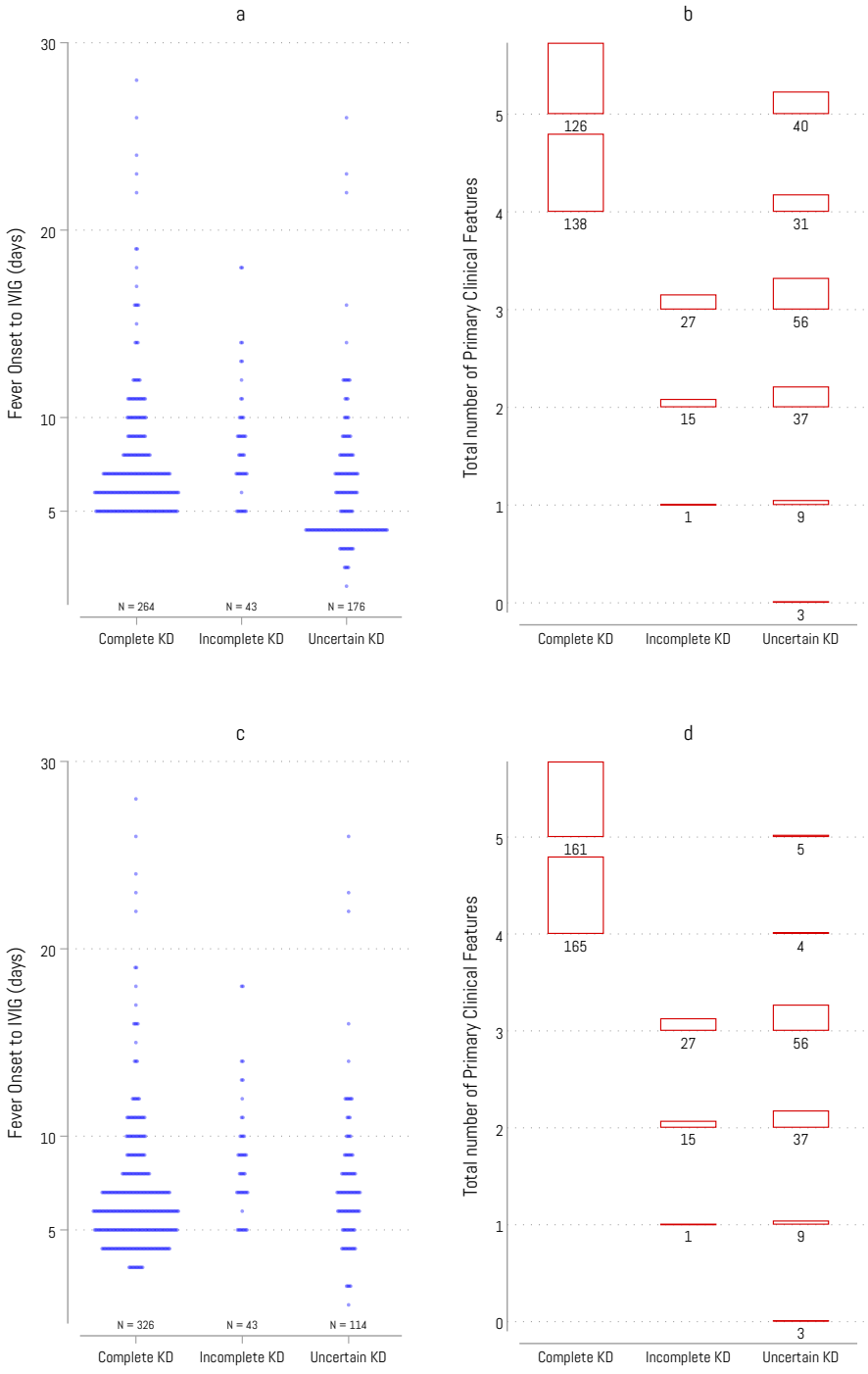


Figure 6.2:
Strict versus Permissive Definition of Complete Kawasaki Disease

a. Time from fever onset to first dose of IVIG by diagnostic category, where the diagnosis of 'Complete KD' requires 5 or more days of fever.
b. Total number of Primary Clinical Features of KD by diagnostic category, where the diagnosis of 'Complete KD' requires 5 or more days of fever.
c. Time from fever onset to first dose of IVIG by diagnostic category, where the diagnosis of 'Complete KD' can be made with as few as 3 days of fever.
d. Total number of Primary Clinical Features of KD by diagnostic category, where the diagnosis of 'Complete KD' can be made with as few as 3 days of fever.
IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Treatment and Response

IVIG was given to 99.2% (479/483) of patients, with the majority (93.3%, 429/460*) receiving the recommended dose of 2 g/kg; IVIG dosing did not differ between the diagnostic groups (**Table 6.1**). IVIG was given on or before day 5 of fever in 33.9% (158/466) of patients, and after day 10 of fever in 16.5% (77/466) of patients. The median infusion duration was 8.0 hours (IQR 6.8–10.2 hours). Adverse events related to IVIG were infrequent (occurring in

* This is the number for whom a dose in grams/kg was known.

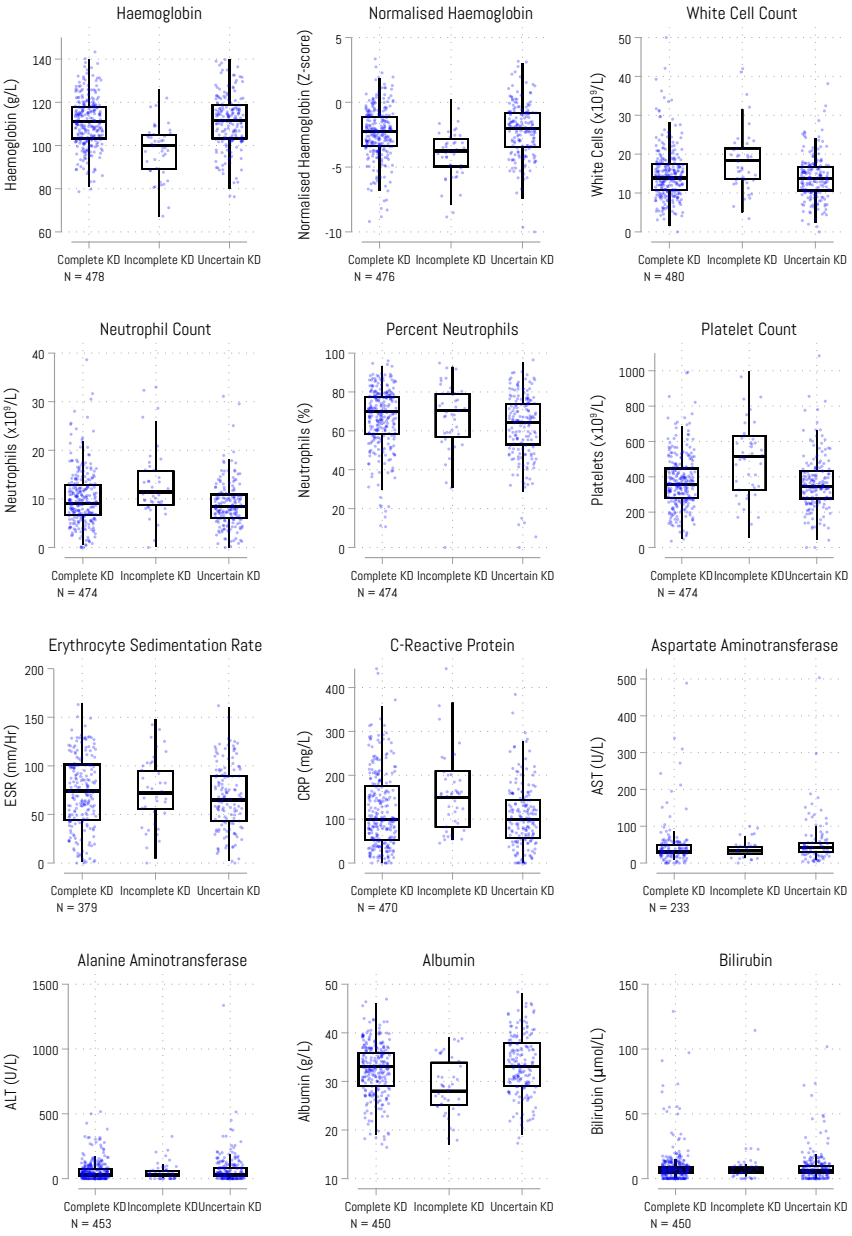


Figure 6.3:
Laboratory Markers of Children Diagnosed with Kawasaki Disease, by Diagnostic Category

Results are from blood samples taken prior to the administration of IVIG. Complete KD: fever for ≥5 days plus ≥4/5 cardinal clinical features. Incomplete KD was diagnosed according to the algorithm in McCrindle *et al*, 2017.6 Children who met inclusion criteria but who did not meet the criteria for Complete KD or Incomplete KD were classified as Uncertain KD.

20.5%, 98/479) and typically mild (**Supplementary Table 6.2**). The most frequently reported was fever, described in 11.9% (57/479).

Aspirin was prescribed in 97.3% (470/483) of patients, with most (86.9%, 399/459) only ever receiving low-dose aspirin (3–5 mg/kg/day). Aspirin dosing clustered within the low-dose but not the moderate- or high-dose ranges (**Supplementary Figure 6.1**); we therefore analysed aspirin dosing as below or above 10 mg/kg/day. Aspirin dosing differed markedly between sites: three large hospitals—accounting for 57.8% (279/483) of the cohort—did not use aspirin at doses >10 mg/kg/day (**Supplementary Table 6.3**). Children given aspirin at >10 mg/kg/day did not differ from those given ≤10 mg/kg/day in terms of sex, age, diagnostic category, number of cardinal clinical features, or rates of admission to intensive care (**Supplementary Table 6.4**). Those given a

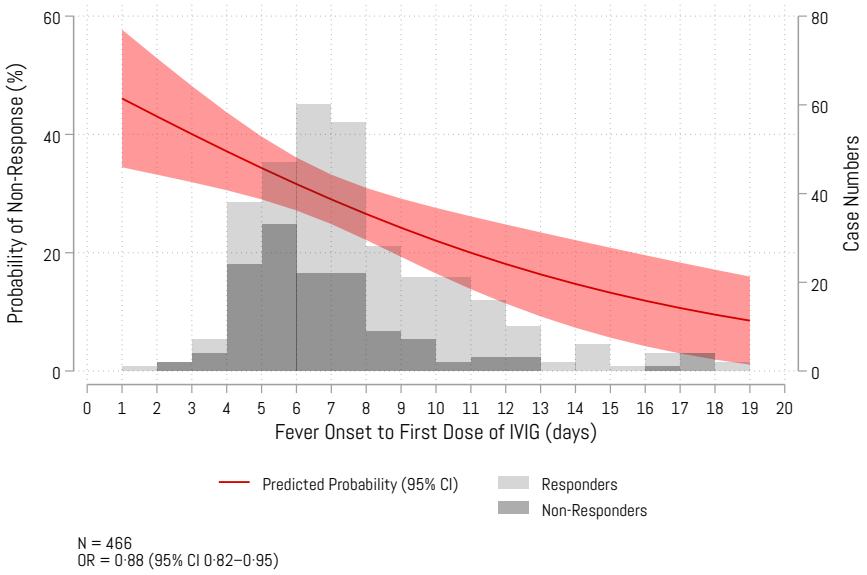


Figure 6.4: Probability of Non-Response to Treatment of Kawasaki Disease with Intravenous Immunoglobulin, by Time to Treatment

Predicted probability of non-response to treatment with IVIG by time from fever onset to treatment with IVIG (as estimated using non-parametric logistic regression). The histogram shows case numbers at each day between fever onset and the first dose of IVIG. IVIG, intravenous immunoglobulin.

higher dose of aspirin were more likely to have been transferred from another hospital (35% *versus* 19%, $p = 0.021$) and had higher rates of non-response to primary therapy with IVIG (48% *versus* 28%, $p = 0.015$); they were also more likely to have coronary artery aneurysms at presentation ($p < 0.001$, see **Supplementary Table 6.4**).

Corticosteroids were used as adjuvant primary therapy in 10.8% (52/483) of patients; oral prednisolone was preferred (75% received oral prednisolone alone or in combination with intravenous corticosteroid), typically at a dose of 1–2 mg/kg/day (median 1.9, IQR 1.1–2.0) (**Table 6.1**).

Non-response to primary therapy with IVIG occurred in 29.0% of patients (139/479, **Table 6.2**). The diagnosis was based on persistent or recurrent fever in 89% of non-responders (123/139)—frequently less than 36 hours after the end of the IVIG infusion (59%, 65/110*). Children who received IVIG after day 5 of fever were significantly less likely to require additional therapy than those treated on or before day 5 (24% [73/308] *versus* 40% [63/158], $p < 0.001$). Time from fever onset to the first dose of IVIG was the only clinical variable that predicted treatment non-response (**Figure 6.4**, **Supplementary Table 6.5**). Days from fever onset to IVIG administration was included in a logistic regression model with age, sex, and number of cardinal clinical features; the odds ratio was 0.88 (95% CI 0.82–0.95), indicating that children treated earlier had higher odds of treatment failure (**Figure 6.4**, **Supplementary Table 6.6**). Neutrophil fraction and C-reactive protein (CRP) were significantly higher in non-responders as compared with responders, whereas platelet count and albumin were significantly lower (**Supplementary Table 6.6**). These

* This is the number for whom the time from the end of the IVIG infusion to the decision to retreat was known.

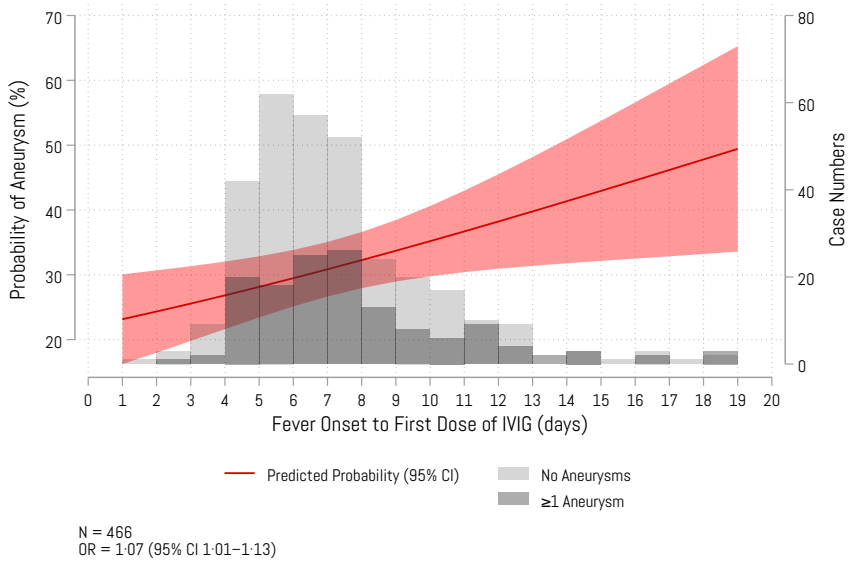


Figure 6.5:
Probability of Coronary Aneurysms in Children Diagnosed with Kawasaki Disease, by Time to Treatment

Predicted probability of developing coronary artery aneurysms (defined here as a coronary artery Z-score ≥5) by time from fever onset to treatment with IVIG (as estimated using non-parametric logistic regression). The histogram shows case numbers at each day between fever onset and the first dose of IVIG. IVIG, intravenous immunoglobulin.

correlations were independent of time from fever onset to blood sampling (**Supplementary Figure 6.2**). The best predictors of treatment non-response were albumin and CRP before day 5 of fever (**Supplementary Figure 6.2**). There was no difference in IVIG dosing between responders and non-responders (**Supplementary Table 6.5**).

The most frequent approach to secondary therapy was further IVIG (given to 89% of non-responders, 123/139), followed by corticosteroids (32%, 44/139). In contrast to their use as primary adjunctive therapy, corticosteroids used as secondary therapy were more frequently given intravenously: of those given corticosteroids 77% received intravenous methylprednisolone alone or in combination with oral steroid (**Supplementary Table 6.7**).

Coronary Artery Outcomes

Inpatient echocardiogram reports were available for 82.2% of patients (397/483), and outpatient echocardiogram reports for 79.3% (383/483; **Table 6.5**). Mild-to-moderate coronary artery dilatation (coronary artery Z-score of 2 to 5) was seen in 29.2% of inpatient echocardiograms (103/353), while medium-to-large aneurysms (Z-score ≥5) were only seen in 6.5% (23/353). Medium-to-large aneurysms were significantly more frequent among those with incomplete KD than the other groups on both echocardiograms (**Table 6.5**, **Supplementary Figure 6.3**). The risk of moderate-to-large aneurysms on the echocardiogram at presentation was correlated with time-to-treatment (**Figure 6.5**, **Supplementary Figure 6.4**); Large aneurysms (Z-score ≥10) were not observed before day 10 of fever (**Figure 6.6**). Coronary artery outcomes did not differ by response to treatment (**Supplementary Table 6.8**) or with laboratory markers (**Figure 6.7**).

Figure 6.6:
Maximum Coronary Artery Dimensions of Children Diagnosed with Kawasaki Disease, by Day of Echocardiogram

Each point represents the maximum dimension (Z-score) of a single vessel, as measured by echocardiogram during the acute admission. Red points indicate vessels that went on to have a Z-score <5 at 6–8 week follow-up, whereas blue dots indicate vessels that had a Z-score ≥5 at follow-up.

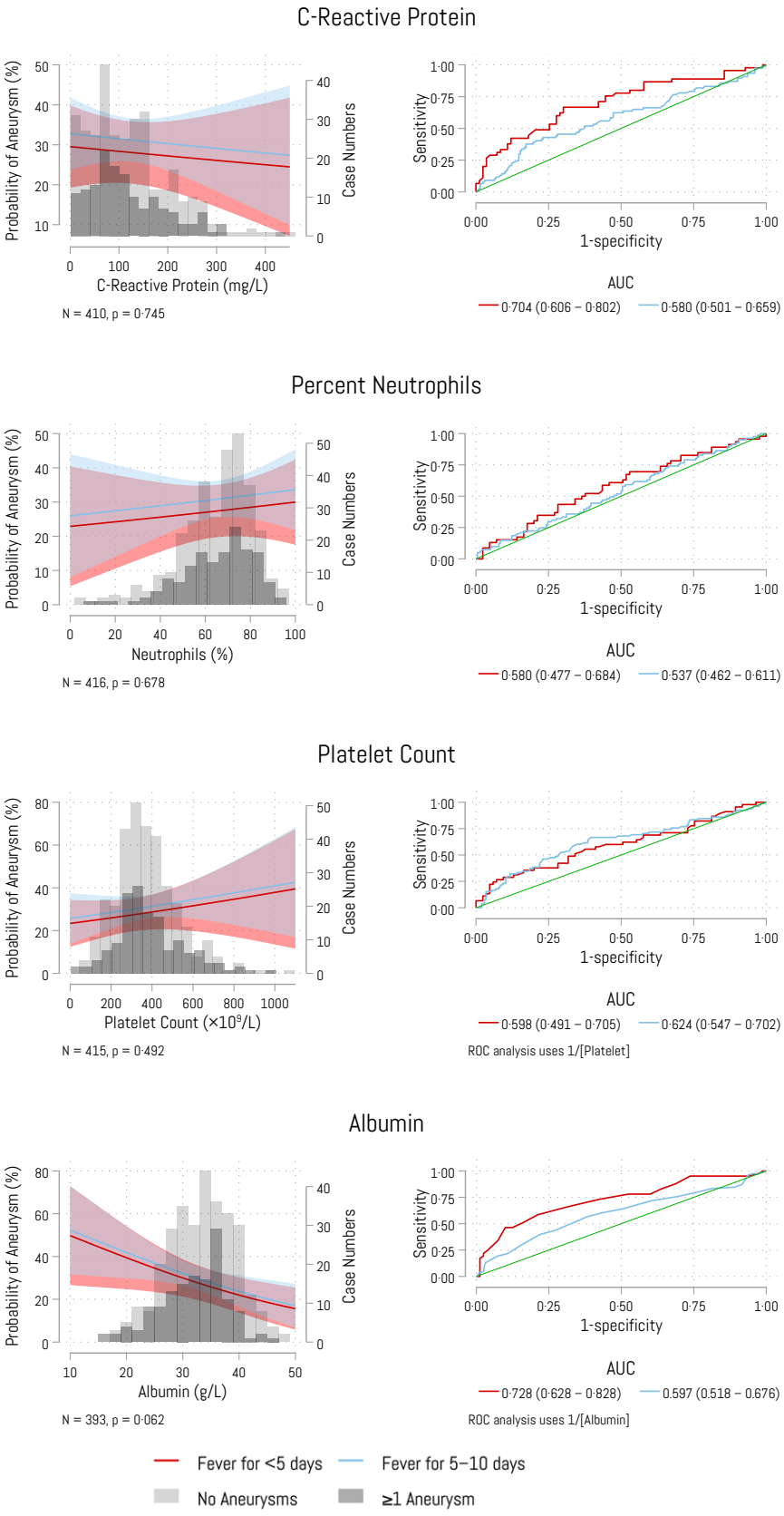


Figure 6.7:
Probability of Coronary Aneurysms in Children Diagnosed with Kawasaki Disease, by Laboratory Markers

Each graph on the left depicts the predicted probability of coronary artery aneurysm (defined here as a coronary artery Z-score ≥5) on the echocardiogram at presentation (as estimated using non-parametric logistic regression), superimposed on a histogram of case numbers at each interval for that laboratory variable. Each graph on the left depicts the receiver-operator characteristic (ROC) curve for each laboratory variable as a predictor of coronary artery aneurysms.

Table 6.1: Baseline Demographic and Clinical Characteristics of Children Diagnosed with Kawasaki Disease, by Diagnostic Category

	Diagnostic Category			Total	
	Complete KD	Incomplete KD	Uncertain KD		P
	N = 264	N = 43	N = 176	N = 483	
Clinical Characteristics					
Male	152/264 (57.6%)	27/43 (63%)	108/176 (61%)	287/483 (59.4%)	0.65
Age (years)	3.1 (1.4–4.8)	1.5 (0.4–3.2)	2.8 (1.3–4.6)	2.8 (1.3–4.6)	0.002
0–1	36/264 (13.6%)	19/43 (44%)	35/176 (20%)	90/483 (18.6%)	<0.001
1–4	166/264 (62.9%)	18/43 (42%)	103/176 (59%)	287/483 (59.4%)	
5–9	51/264 (19.3%)	6/43 (14%)	33/176 (19%)	90/483 (18.6%)	
10–14	11/264 (4.2%)	0/43 (0%)	5/176 (3%)	16/483 (3.3%)	
Indigenous	6/264 (2.3%)	1/43 (2%)	4/176 (2%)	11/483 (2.3%)	1.00
Mother's Place of Birth					
Africa	2/264 (0.8%)	0/43 (0%)	3/176 (2%)	5/483 (1.0%)	0.29
Americas	2/264 (0.8%)	0/43 (0%)	1/176 (1%)	3/483 (0.6%)	
Asia	70/264 (26.5%)	16/43 (37%)	50/176 (30%)	138/483 (28.6%)	
Europe	7/264 (2.7%)	1/43 (2%)	4/176 (2%)	12/483 (2.5%)	
Oceania	76/264 (28.8%)	13/43 (30%)	33/176 (19%)	122/483 (25.3%)	
Unknown	107/264 (40.5%)	13/43 (30%)	83/176 (47%)	203/483 (42.0%)	
Interhospital transfer	51/264 (19.3%)	14/43 (33%)	31/176 (18%)	96/483 (19.9%)	0.052
GP/ED presentations in week before admission	2 (1–3)	2 (1–2)	2 (1–2)	2 (1–3)	0.096
Days from fever onset to hospital admission	5 (4–7)	6 (4–8)	4 (3–6)	5 (3–7)	<0.001
Number of Cardinal Clinical Criteria	4 (4–5)	3 (2–3)	3 (2–4)	4 (3–5)	<0.001
5	126/264 (47.7%)	0/43 (0%)	40/176 (23%)	166/483 (34.4%)	<0.001
4	138/264 (52.3%)	0/43 (0%)	31/176 (18%)	169/483 (35.0%)	
3	0/264 (0.0%)	27/43 (63%)	56/176 (32%)	83/483 (17.2%)	
2	0/264 (0.0%)	15/43 (35%)	37/176 (21%)	52/483 (10.8%)	
1	0/264 (0.0%)	1/43 (2%)	9/176 (5%)	10/483 (2.1%)	
0	0/264 (0.0%)	0/43 (0%)	3/176 (2%)	3/483 (0.6%)	
Specific Cardinal Clinical Criteria					
Rash	254/264 (96.2%)	30/43 (70%)	144/176 (82%)	428/483 (88.6%)	<0.001
Oro-mucosal changes	246/264 (93.2%)	25/43 (58%)	115/176 (65%)	386/483 (79.9%)	<0.001
Conjunctival injection	253/264 (95.8%)	32/43 (74%)	130/176 (74%)	415/483 (85.9%)	<0.001
Cervical lymphadenopathy	213/264 (80.7%)	15/43 (35%)	95/176 (54%)	323/483 (66.9%)	<0.001
Peripheral changes	216/264 (81.8%)	10/43 (23%)	91/176 (52%)	317/483 (65.6%)	<0.001

Continued...

Table 6.1 continued...

Laboratory Variable, Median (IQR) [n/N]					
Haemoglobin (g/L)	111 (103–118) [261/264]	100 (91–105) [43/43]	112 (103–119) [174/176]	110 (102–118) [478/483]	<0.001
Normalised Haemoglobin (Z–score)	-2.4 (2.0) [260/264]	-3.9 (1.9) [43/43]	-2.2 (2.1) [174/176]	-2.4 (2.1) [476/483]	<0.001
White Cells ($\times 10^9$/L)	13.9 (10.6–17.6) [263/264]	16.9 (13.2–21.4) [43/43]	13.7 (10.5–16.8) [174/176]	14.1 (10.8–17.9) [480/483]	0.001
Neutrophils ($\times 10^9$/L)	9.1 (6.5–12.9) [261/264]	11.4 (8.3–15.3) [42/43]	8.5 (6.1–11.0) [171/176]	9.0 (6.5–12.3) [474/483]	<0.001
Neutrophils (%)	70 (58–78) [261/264]	69 (56–79) [42/43]	64 (53–74) [171/176]	68 (56–77) [474/483]	0.021
Platelets ($\times 10^9$/L)	355 (274–450) [260/264]	514 (324–628) [42/43]	344 (273–431) [172/176]	358 (277–458) [474/483]	<0.001
ESR (mm/Hr)	74 (44–102) [207/264]	72 (55–95) [37/43]	64 (43–90) [135/176]	70 (44–95) [379/483]	0.37
CRP (mg/L)	100 (52–176) [259/264]	147 (81–208) [43/43]	100 (57–146) [168/176]	104 (59–167) [470/483]	0.001
AST (U/L)	32 (25–50) [129/264]	34 (24–47) [25/43]	42 (29–57) [79/176]	36 (26–51) [233/483]	0.068
ALT (U/L)	31 (17–78) [249/264]	30 (16–64) [43/43]	30 (16–88) [161/176]	30 (17–70) [453/483]	0.91
Albumin (g/L)	33 (29–36) [247/264]	28 (25–34) [42/43]	33 (29–38) [161/176]	33 (28–36) [450/483]	<0.001
Bilirubin (μmol/L)	6 (4–9) [247/264]	6 (4–9) [42/43]	6 (4–10) [161/176]	6 (4–10) [450/483]	0.40
Treatment Modalities					
IVIG	**264/264 (100.0%)**	**45/43 (100%)**	**170/176 (98%)**	**479/483 (99.2%)**	0.028
1 g/kg	9/256 (3.5%)	1/39 (3%)	5/165 (3%)	15/460 (3.3%)	0.90
2 g/kg	237/256 (92.6%)	36/39 (92%)	154/165 (95%)	429/460 (93.3%)	
Other dose	10/256 (3.9%)	2/39 (5%)	4/165 (2%)	16/460 (3.5%)	
Unknown	8/264 (3.0%)	4/43 (9%)	7/176 (4%)	19/479 (4.0%)	0.18
Days from fever onset to IVIG	7 (6–8)	8 (7–10)	5 (4–7)	6 (5–8)	<0.001
Aspirin	**256/264 (97.0%)**	**42/43 (98%)**	**172/176 (98%)**	**470/483 (97.3%)**	0.97
3–5 mg/kg/day	219/252 (86.9%)	36/40 (85%)	144/167 (87%)	399/459 (86.9%)	0.97
30–50 mg/kg/day	9/252 (3.6%)	1/40 (3%)	5/167 (3%)	15/459 (3.3%)	
80–100 mg/kg/day	1/252 (0.4%)	0/40 (0%)	0/167 (0%)	1/459 (0.2%)	
Other dose	23/252 (9.1%)	5/40 (13%)	16/167 (10%)	44/459 (9.6%)	
Unknown	4/256 (1.6%)	2/42 (5%)	5/170 (3%)	11/470 (2.3%)	0.39
Corticosteroids	**25/264 (9.5%)**	**8/43 (19%)**	**19/176 (11%)**	**52/483 (10.8%)**	**0.25**
Oral only	15/25 (60.0%)	2/8 (25%)	9/19 (47%)	26/52 (50.0%)	0.22
Intravenous only	3/25 (12.0%)	4/8 (50%)	6/19 (32%)	13/52 (25.0%)	
Oral and Intravenous	7/25 (28.0%)	2/8 (25%)	4/19 (21%)	13/52 (25.0%)	
Anticoagulant	**3/264 (1.1%)**	**3/45 (7%)**	**0/174 (0%)**	**6/483 (1.2%)**	**0.001**
Enoxaparin	2/3 (66.7%)	3/3 (100%)	– (–)	5/6 (83.3%)	0.27
Warfarin	1/3 (33.3%)	0/3 (0%)	– (–)	1/6 (16.7%)	0.27

Diagnosis of Complete KD required fever for ≥5 days plus ≥4/5 cardinal clinical features. Incomplete KD was diagnosed according to the algorithm in McCrindle *et al*, 2017.1 Children who met inclusion criteria but who did not meet the criteria for Complete KD or Incomplete KD were classified as Uncertain KD. Laboratory data are from blood samples taken prior to the administration of IVIG. Categorical data are summarised as frequency (%) and compared using Pearson's $\chi 2$ statistic. Continuous data are summarised as median (interquartile range) and compared using the Kruskal–Wallis test—except for the normalised haemoglobin, which is summarised as mean (standard deviation) and compared using ANOVA. ALT, alanine transaminase; AST, aspartate transaminase; CRP, C–reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate. GP, general practitioner; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Table 6.2: Clinical Outcomes of Children Diagnosed with Kawasaki Disease, by Diagnostic Category

	Diagnostic Category			Total	
	Complete KD	**Incomplete KD**	**Uncertain KD**		**P**
Treatment Outcomes					
Non-Response to Primary Therapy	72/264 (27.3%)	13/43 (30%)	54/172 (31%)	139/479 (29.0%)	0.64
Persistent / recurrent fever	67/72 (93%)	10/13 (77%)	46/54 (85%)	123/139 (89%)	0.15
Hours post-IVIG	32 (22–42)	90 (74–104)	29 (12–34)	32 (18–44)	0.004
Persistent / recurrent clinical features	30/72 (42%)	5/13 (39%)	27/54 (50%)	62/139 (45%)	0.58
Hours post-IVIG	32 (24–40)	70 (29–104)	34 (14–50)	34 (24–46)	0.48
Raised inflammatory markers	17/72 (24%)	6/13 (46%)	17/54 (32%)	40/139 (29%)	0.22
Hours post-IVIG	30 (24–38)	101 (62–144)	32 (24–41)	32 (24–42)	0.10
Admission Outcomes					
Admitted to ICU/HDU	13/264 (4.9%)	4/43 (9%)	8/176 (5%)	25/483 (5.2%)	0.43
Respiratory Support	5/13 (39%)	1/4 (25%)	3/8 (38%)	9/25 (36%)	0.88
Blood Pressure Support	6/13 (46%)	2/4 (50%)	3/8 (38%)	11/25 (44%)	0.90
ECMO	0/13 (0%)	0/4 (0%)	1/8 (13%)	1/25 (4%)	0.33
Total admitted days	11 (8–15)	14 (12–26)	10 (8–14)	12 (8–15)	0.11
Acute Coronary Artery Outcomes					
Inpatient Echocardiogram	217/264 (82.2%)	36/43 (84%)	142/176 (81%)	397/483 (82.2%)	0.52
Fever Onset to Echocardiogram (days)	8 (6–10)	8 (7–12)	6 (5–9)	8 (6–10)	<0.001
Worst Coronary Artery Z–score					
<2	125/188 (67%)	12/34 (35%)	90/131 (69%)	227/353 (64.3%)	<0.001
2 to <2.5	13/188 (7%)	3/34 (9%)	18/131 (14%)	34/353 (9.6%)	
2.5 to <5	39/188 (21%)	12/34 (35%)	18/131 (14%)	69/353 (19.5%)	
5 to <10	8/188 (4%)	3/34 (9%)	5/131 (4%)	16/353 (4.5%)	
≥10	3/188 (3%)	4/34 (12%)	0/131 (0%)	7/353 (2.0%)	
Subacute Coronary Artery Outcomes					
Follow–Up Echocardiogram	214/264 (81.1%)	35/43 (81%)	134/176 (76%)	383/483 (79.3%)	0.79
Discharge to Echocardiogram (weeks)	6 (5–8)	7 (5–12)	6 (5–8)	6 (5–8)	0.071
Worst Coronary Artery Z–score					
<2	142/183 (78%)	17/30 (57%)	105/118 (89%)	264/331 (79.8%)	<0.001
2 to <2.5	16/183 (9%)	2/30 (7%)	6/118 (5%)	24/331 (7.3%)	
2.5 to <5	16/183 (9%)	4/30 (13%)	7/118 (6%)	27/331 (8.2%)	
5 to <10	5/183 (3%)	1/30 (3%)	0/118 (0%)	6/331 (1.8%)	
≥10	4/183 (2%)	6/30 (20%)	0/118 (0%)	10/331 (3.0%)	

Diagnosis of Complete KD required fever for ≥5 days plus ≥4/5 cardinal clinical features. Incomplete KD was diagnosed according to the algorithm in McCrindle *et al*, 2017.1 Children who met inclusion criteria but who did not meet the criteria for Complete KD or Incomplete KD were classified as Uncertain KD. Wherever possible coronary artery Z-scores were re-calculated using the method of Dallaire & Dahdah (Dallaire F, Dahdah N. New Equations and a Critical Appraisal of Coronary Artery Z Scores in Healthy Children. Journal of the American Society of Echocardiography. 2011 Jan;24(1):60–74); where this was not possible, but a Z-score had been documented, the documented Z-score was used. Categorical data are summarised as frequency (%) and compared using Pearson's $\chi 2$ statistic. Continuous data are summarised as median (interquartile range) and compared using the Kruskal-Wallis test. ECMO, extracorporeal membrane oxygenation; ICU/HDU, intensive care unit / high dependency unit.

Discussion

We report findings from a large, prospective, multi-centre surveillance network recruiting children admitted to referral hospitals with clinician-diagnosed KD. This is the largest cohort of children with KD from the Southern Hemisphere, and one of the largest prospectively recruited KD cohorts outside of Asia.

Australian guidelines use the AHA criteria[1] for the diagnosis of KD, yet over one third of the patients in our cohort did not fulfil those criteria for either Complete or Incomplete KD. Even when the less rigorous definition for Complete KD (allowing for the diagnosis to be made with as few as 3 days of fever in the setting of four or more cardinal clinical features) was applied, almost one quarter did not meet criteria for either diagnosis. There were no significant differences in clinical or laboratory variables between those with Complete versus Uncertain KD, however comparatively few coronary artery lesions were observed in the latter group. It is possible that a significant proportion of the children who did not fulfil the diagnostic criteria for KD had an alternative process underlying their presentation.

The rate of treatment failure in this cohort was is higher than has been described in similar studies[1,15–17]. This may be a result of how the diagnosis of treatment failure was made, as most of the diagnoses of treatment failure on the basis of persistent or recurrent fever were given less than 36 hours after the end of the IVIG infusion. There is currently no consensus definition of treatment failure in KD. The AHA statement uses 'IVIG Resistance' to refer to the persistence or recurrence of fever "...*at least* 36 hours after the end of [the] IVIG infusion" (emphasis added),[1] however the term "at least" is sometimes omitted when that definition is cited.[15] Those with treatment failure in our cohort were not at increased risk for coronary artery aneurysms. This is in contrast to previous observations that treatment failure was associated with higher rates of coronary artery aneurysms.[18,19] One possible explanation for this observation is that treatment failure was over diagnosed in Australia. Over diagnosis of treatment failure risks exposing children to additional medical procedures and blood products and expends scarce resources. There is a need for a clear well communicated consensus definition of treatment failure.

The high proportion of children started on aspirin in the 'anti-platelet' low-dose range (3–5 mg/kg) rather than the 'anti-inflammatory' moderate- or high-dose ranges (30–50 or 80–100 mg/kg) is strikingly different from that described in other studies,[20,21] but aligns with Australian guidelines and the survey-reported preferences of Australian clinicians, as previously described.[22,23] Moderate- or high-dose aspirin has never been shown to improve outcomes in KD.[24–27] Some authors have reported that the use of low-dose aspirin was associated with a higher risk of treatment non-response,[28]

however this association has not been replicated in large studies nor in a recent meta-analysis.[26,27,29] The authors of that meta-analysis noted that although the time to resolution of fever was shorter among those receiving high-dose aspirin compared with low-dose aspirin, this might merely indicate an antipyretic effect rather than a signal of treatment failure.[26] Moreover, that meta-analysis found that the current weight of evidence suggests that aspirin dose does not influence the development of coronary artery aneurysms and there is no trial-level evidence to support its widespread use.[26] We do not believe that the high rates of treatment failure that we observed were attributable to the use of low-dose aspirin as those who received higher doses of aspirin had higher rates of treatment non-response.

Early use of IVIG was common and significantly associated with higher rates of treatment failure. The association between early IVIG treatment failure in KD has been reported in several studies.[30–33] The use of IVIG observed in this study was largely in line with both local and international guidelines[23,34]: over 99% of patients received IVIG, of whom over 90% were given a dose of 2 g/kg. While one third of infusion-related adverse events were generally rare, fever during the infusion was frequently reported. Fever during the infusion may simply reflect the underlying systemic inflammatory process, but may prompt interruption of the infusion in line with national guidelines for the management of suspected transfusion reactions[35]—potentially resulting in sub-optimal IVIG dosing for children with KD. Given that serious infusion reactions appear to be uncommon, there may be scope to clarify infusion protocols for children receiving IVIG for KD.

This study has several limitations. The recruitment sites were major referral centres and included seven out of the eight specialist paediatric hospitals in the country. Since smaller units frequently use clinical practice guidelines from (or seek advice from) their referral paediatric hospital, we are reasonably confident that the treatment practices that we described are broadly generalisable to Australia as a whole. Surveillance was largely independent of treating teams and relied on clinical documentation to infer diagnostic and treatment decisions, which in the face of sparse or ambiguous documentation was challenging. We collaborated with a well-established paediatric acute illness surveillance network with over a decade of experience in case identification and data acquisition, and with established protocols for confirming data quality.[8] Without a gold-standard diagnostic test the diagnosis of KD presents complex challenges. Many of the children in our cohort did not fulfil the diagnostic criteria for KD, however our ability to retrospectively classify cases by diagnostic category presented an opportunity to better understand diagnostic and therapeutic practices on the ground. We were also limited by the focus on the acute KD presentation: we did not seek to reassess children in the subacute phase when signs such as periungual

desquamation (a diagnostic feature if peripheral changes are not present in the acute illness[1]) may have been present. It is also possible that for some children an alternative diagnosis (such as systemic juvenile idiopathic arthritis) may have become apparent after diagnosis, which may not have been captured.

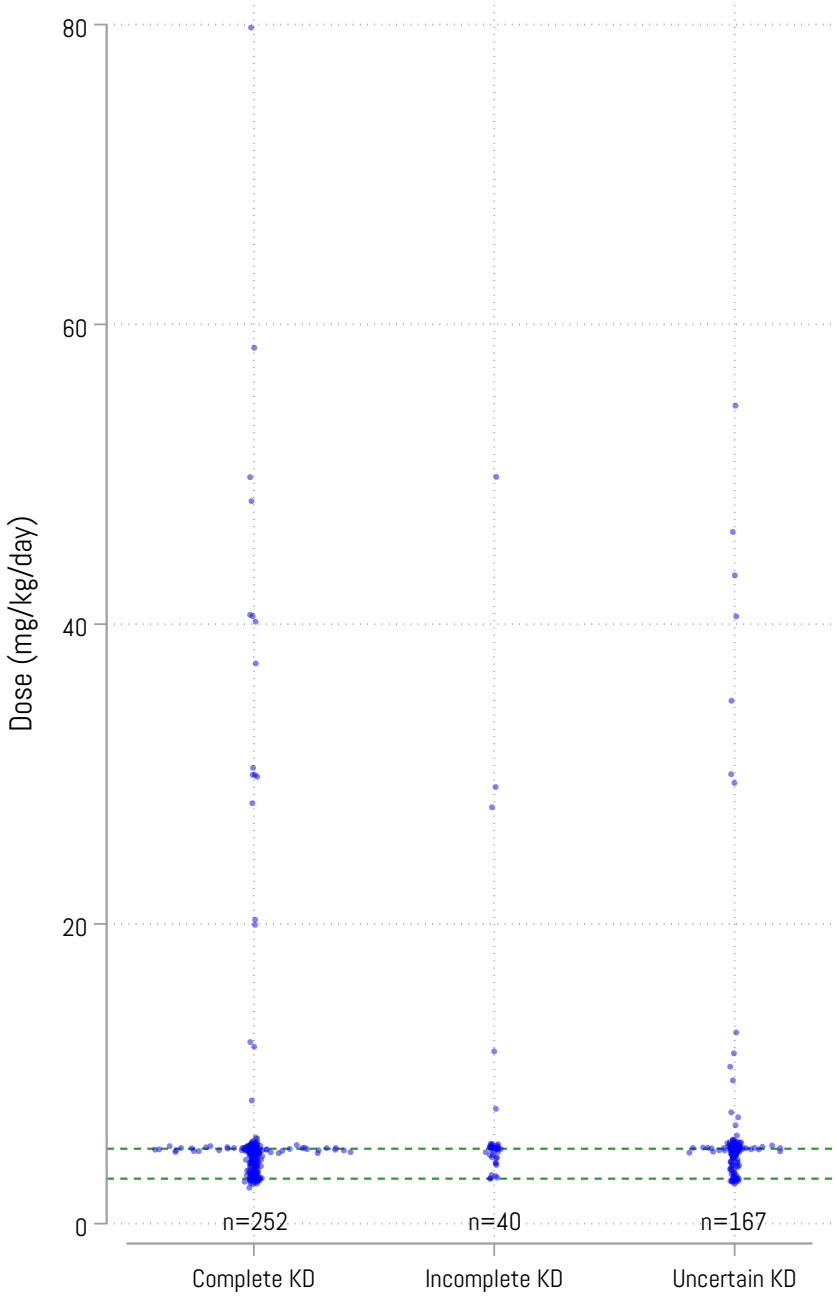
Conclusions

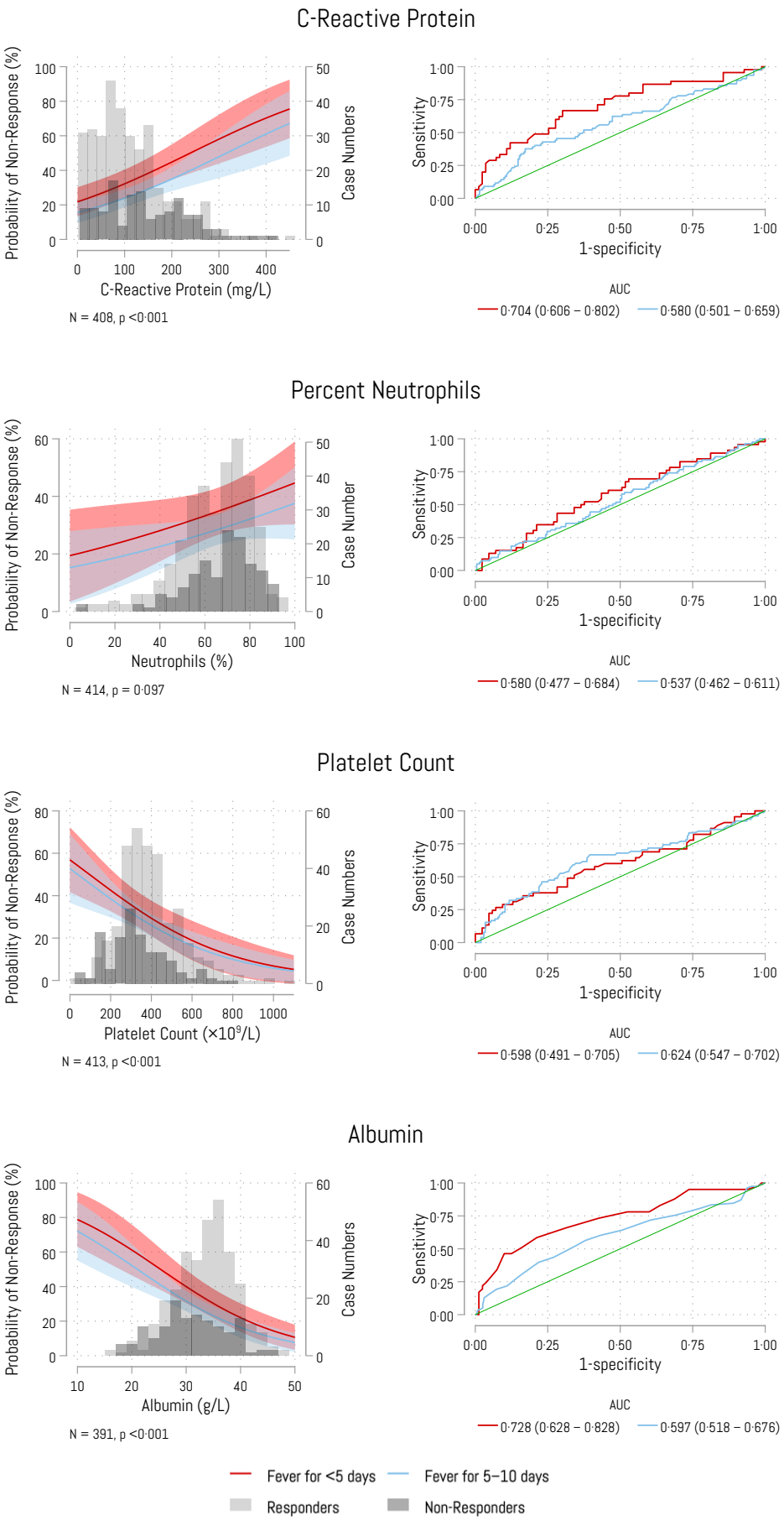
We report demographic, clinical, and treatment data from a large, prospective surveillance study of KD in Australia. KD was frequently diagnosed in children who did not fulfil diagnostic criteria, and the rate of treatment failure was higher than has been reported elsewhere. Observed practice with regards to aspirin dosing also differed markedly from both international guidelines and practice but was better aligned with published evidence. International collaboration is needed to better define IVIG non-responsiveness in the treatment of KD and to better understand the underlying mechanisms of this phenomenon.

Supplementary Results

Supplementary Figure 6.1: Aspirin Dosing for Children Diagnosed with Kawasaki Disease, by Diagnostic Category

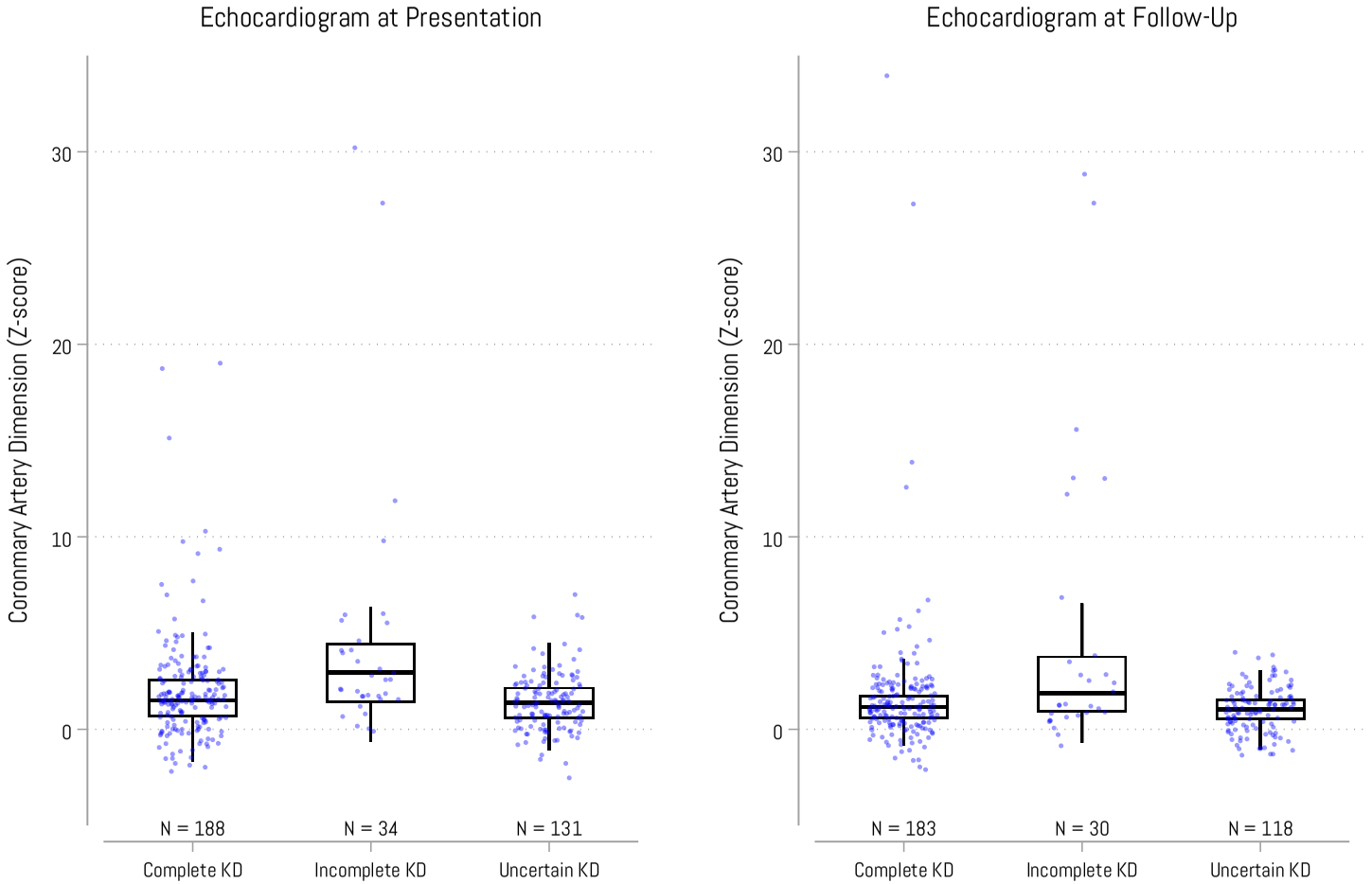
First dose of aspirin prescribed during KD episode. Dashed green lines represent the "low dose" range of 3–5 mg/kg/day. Diagnosis of Complete KD required fever for ≥5 days plus ≥4/5 cardinal clinical features. Incomplete KD was diagnosed according to the algorithm in McCrindle *et al*, 2017. Children who met inclusion criteria but who did not meet the criteria for Complete KD or Incomplete KD were classified as Uncertain KD.





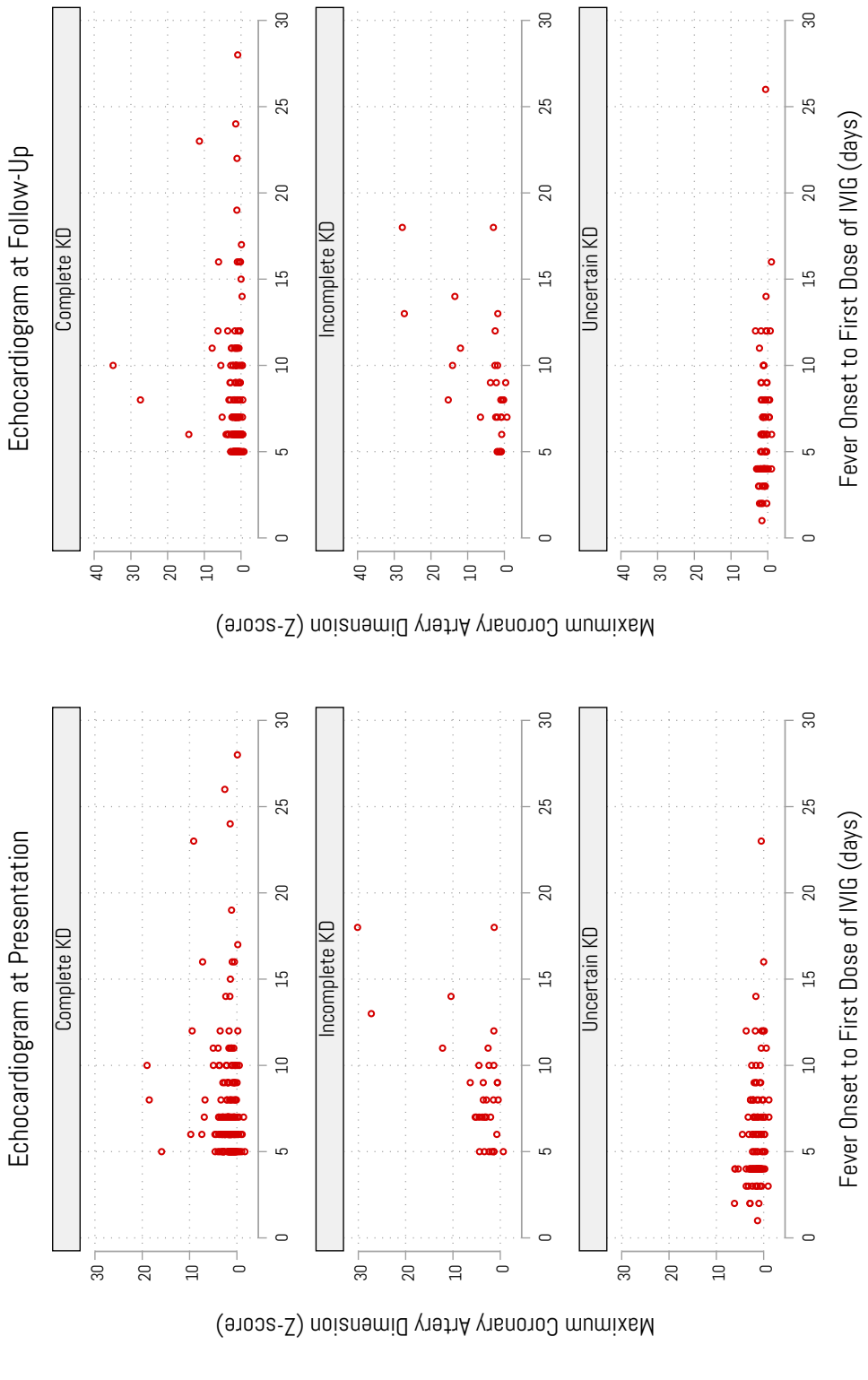
Supplementary Figure 6.2: Probability of Non-Response to Treatment of Kawasaki Disease with Intravenous Immunoglobulin, by Laboratory Markers

Each graph on the left depicts the predicted probability of non-response to treatment with intravenous immunoglobulin (as estimated using non-parametric logistic regression), superimposed on a histogram of case numbers at each interval for that laboratory variable. Each graph on the left depicts the receiver-operator characteristic (ROC) curve for each laboratory variable as a predictor of non-response to treatment with intravenous immunoglobulin.



Supplementary Figure 6.3: Coronary Artery Dimensions of Children Diagnosed with Kawasaki Disease at Two Timepoints, by Diagnostic Category

Each point represents the measurement of the largest coronary artery for each child. Diagnosis of Complete KD required fever for ≥5 days plus ≥4/5 cardinal clinical features. Incomplete KD was diagnosed according to the algorithm in McCrindle *et al*, 2017.[6] Children who met inclusion criteria but who did not meet the criteria for Complete KD or Incomplete KD were classified as Uncertain KD.



Supplementary Figure 6.4: Coronary Artery Dimensions of Children Diagnosed with Kawasaki Disease at Two Timepoints, by Time to Treatment

Each point represents the measurement of a coronary artery, such that multiple measurements for each child may be shown. Diagnosis of Complete KD required fever for ≥5 days plus ≥4/5 cardinal clinical features. Incomplete KD was diagnosed according to the algorithm in McCrindle *et al*, 2017.[6] Children who met inclusion criteria but who did not meet the criteria for Complete KD or Incomplete KD were classified as Uncertain KD.

Supplementary Table 6.1: Top 5 Countries of Birth of Children with Kawasaki Disease, and their Parents

Patient		Mother		Father	
1. Australia	435/471 (92.4%)	1. Australia	116/280 (41.4%)	1. Australia	101/267 (37.8%)
2. China	8/471 (1.7%)	2. China	59/280 (21.1%)	2. China	54/267 (20.2%)
3. India	5/471 (1.1%)	3. India	15/280 (5.4%)	3. India	17/267 (6.4%)
4. Hong Kong	3/471 (0.6%)	4. Japan	8/280 (2.9%)	4. Vietnam	8/267 (3.0%)
4. US	3/471 (0.6%)	5. Afghanistan	7/280 (2.5%)	5. South Korea	7/267 (2.6%)
5. Japan	2/471 (0.4%)	5. Vietnam	7/280 (2.5%)		
5. South Korea	2/471 (0.4%)				
5. Singapore	2/471 (0.4%)				

Denominators indicate the number of cases for which the country of birth was known.

Supplementary Table 6.2: Intravenous Immunoglobulin Infusion-Related Adverse Events

Received IVIG	479
Any Reaction	98 (20.5)
Fever	57 (11.9)
Headache	7 (1.5)
Abdominal Pain	3 (0.6)
Hypotension	9 (1.9)
Anaphylaxis	1 (0.2)
Dizziness	1 (0.2)
Chills	7 (1.5)
Haemolysis	9 (1.9)
Thrombotic Event	1 (0.2)
Renal Failure	1 (0.2)
Other	75 (15.7)

The occurrence of fever during the infusion was not specifically sought in the case reporting form as fever is expected as part of the underlying KD. Fever presented here was documented in a free-text field (see Supplementary Methods: Case Reporting Form). Results are given as frequency (%). IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Supplementary Table 6.3: Aspirin Dosing, by Recruitment Site

	Aspirin Dose		
Site	≤10 mg/kg/day	>10 mg/kg/day	*P*
CHW (N = 08)	108/108 (100%)	0/108 (0%)	<0.001
RCH (N = 115)	115/115 (100%)	0/115 (0%)	
QCH (N = 55)	46/55 (84%)	9/55 (16%)	
PCH (N = 51)	51/51 (100%)	0/51 (0%)	
RDH (N = 6)	3/6 (50%)	3/6 (50%)	
WCH (N = 26)	23/26 (88%)	3/26 (12%)	
MH (N = 62)	60/62 (97%)	2/62 (3%)	
SCH (N = 36)	22/36 (61%)	14/36 (39%)	

CHW, The Children's Hospital at Westmead (Sydney); MH, Monash Hospital (Melbourne); PCH, Perth Children's Hospital; QCH, Queensland Children's Hospital (Brisbane); RCH, Royal Children's Hospital (Melbourne); RDH, Royal Darwin Hospital; SCH, Sydney Children's Hospital; WCH, Women's and Children's Hospital (Adelaide).

Supplementary Table 6.4: Baseline Demographic and Clinical Characteristics of Children Diagnosed with Kawasaki Disease, by Aspirin Dose

	Aspirin Dose		**All**	
	≤10 mg/kg/day	**>10 mg/kg/day**		***P***
	N = 428	**N = 31**	**N = 459**	
Male	258/428 (60.3%)	18/31 (58%)	276/459 (60.1%)	0.808
Age (years)	2.8 (1.3–4.5)	2.1 (0.9–4.9)	2.8 (1.3–4.6)	0.193
0–1	77/428 (18.0%)	9/31 (29%)	86/459 (18.7%)	0.506
1–4	259/428 (60.5%)	16/31 (52%)	275/459 (59.9%)	
5–9	78/428 (18.2%)	5/31 (16%)	83/459 (18.1%)	
10–14	14/428 (3.3%)	1/31 (3%)	15/459 (3.3%)	
Interhospital Transfer	79/428 (18.5%)	11/31 (35%)	90/459 (19.6%)	0.021
GP/ED presentations in week before admission	2 (1–3)	2 (1–2)	2 (1–3)	0.195
Days from fever onset to hospital admission	5 (3–7)	4 (2–6)	5 (3–7)	0.017
Diagnostic Category				
Complete KD	235/428 (54.9%)	17/31 (55%)	252/459 (54.9%)	0.662
Incomplete KD	36/428 (8.4%)	3/31 (13%)	40/459 (8.7%)	
Uncertain KD	157/428 (36.7%)	10/31 (32%)	167/459 (36.4%)	
Total number of Cardinal Clinical Features				
5	148/428 (34.6%)	8/31 (26%)	156/459 (34.0%)	0.123
4	150/428 (35.1%)	13/31 (42%)	163/459 (35.5%)	
3	78/428 (18.2%)	2/31 (6%)	80/459 (17.4%)	
2	40/428 (9.4%)	7/31 (23%)	47/459 (10.2%)	
1	9/428 (2.1%)	1/31 (3%)	10/459 (2.2%)	
0	3/428 (0.7%)	0/31 (0%)	3/459 (0.7%)	
Non-Response to Primary Therapy	118/424 (27.8%)	15/31 (48%)	133/455 (29.2%)	0.015
Admitted to ICU/HDU	18/428 (4.2%)	3/31 (10%)	21/459 (4.6%)	0.159
Worst Coronary Artery Z–score				
<2	211/319 (66.1%)	6/20 (30%)	217/339 (64.0%)	<0.001
2 to <2.5	32/319 (10.0%)	1/20 (5%)	33/339 (9.7%)	
2.5 to <5	59/319 (18.5%)	7/20 (35%)	66/339 (19.5%)	
5 to <10	11/319 (3.5%)	5/20 (25%)	16/339 (4.7%)	
≥10	6/319 (1.9%)	1/20 (5%)	7/339 (2.1%)	

Diagnosis of Complete KD required fever for ≥5 days plus ≥4/5 cardinal clinical features. Incomplete KD was diagnosed according to the algorithm in McCrindle *et al*, 2017.[1] Children who met inclusion criteria but who did not meet the criteria for Complete KD or Incomplete KD were classified as Uncertain KD. Laboratory data are from blood samples taken prior to the administration of IVIG. Categorical data are summarised as frequency (%) and compared using Pearson's $\chi 2$ statistic. Continuous data are summarised as median (interquartile range) and compared using the Kruskal–Wallis test—except for the normalised haemoglobin, which is summarised as mean (standard deviation) and compared using ANOVA.
ALT, alanine transaminase; AST, aspartate transaminase; CRP, C–reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate. GP, general practitioner; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Supplementary Table 6.5: Baseline Demographic and Clinical Characteristics of Children Diagnosed with Kawasaki Disease, by Treatment Response

	Treatment Response		All	
	Responders	Non-Responders		*P*
	N = 340	N = 139	N = 483	
Clinical Characteristics				
Male	203/340 (59.7%)	82/139 (59.0%)	287/483 (59.4%)	0.89
Age (years)	3 (1–4)	3 (2–5)	3 (1–5)	0.11
0–1	68/340 (20.0%)	21/139 (15.1%)	90/483 (18.6%)	0.57
1–4	202/340 (59.4%)	84/139 (60.4%)	287/483 (59.4%)	
5–9	59/340 (17.4%)	29/139 (20.9%)	90/483 (18.6%)	
10–14	11/340 (3.2%)	5/139 (3.6%)	16/483 (3.3%)	
Indigenous	9/340 (2.6%)	2/139 (1.4%)	11/483 (2.3%)	0.41
Interhospital Transfer	62/340 (18.2%)	34/139 (24.5%)	96/483 (19.9%)	0.12
GP/ED presentations in week before admission	2 (1-3)	2 (1-3)	2 (1-3)	0.56
Days from fever onset to hospital admission	5 (4-7)	4 (3-6)	5 (3-7)	0.002
Diagnostic Category				
Complete KD	192/340 (56.5%)	72/139 (51.8%)	264/483 (54.7%)	0.64
Incomplete KD	30/340 (8.8%)	13/139 (9.4%)	43/483 (8.9%)	
Uncertain KD	118/340 (34.7%)	54/139 (38.8%)	176/483 (36.4%)	
Total number of Cardinal Clinical Features				
5	122/340 (35.9%)	44/139 (31.7%)	166/483 (34.4%)	0.78
4	113/340 (33.2%)	56/139 (40.3%)	169/483 (35.0%)	
3	58/340 (17.1%)	22/139 (15.8%)	83/483 (17.2%)	
2	37/340 (10.9%)	14/139 (10.1%)	52/483 (10.8%)	
1	8/340 (2.4%)	2/139 (1.4%)	10/483 (2.1%)	
0	2/340 (0.6%)	1/139 (0.7%)	3/483 (0.6%)	
Specific Cardinal Clinical Criteria				
Rash	299/340 (87.9%)	125/139 (89.9%)	428/483 (88.6%)	0.54
Oro-mucosal changes	277/340 (81.5%)	107/139 (77.0%)	386/483 (79.9%)	0.26
Conjunctival injection	299/340 (87.9%)	115/139 (82.7%)	415/483 (85.9%)	0.13
Peripheral changes	216/340 (63.5%)	98/139 (70.5%)	317/483 (65.6%)	0.14
Cervical lymphadenopathy	227/340 (66.8%)	95/139 (68.3%)	323/483 (66.9%)	0.74

Continued...

Supplementary Table 6.5 continued...

Laboratory Variable Median (IQR) [n/N]	N = 340	N = 139	N = 483	
Haemoglobin (g/L)	111 (103–118) [336/340]	108 (101–118) [138/139]	110 (102–118) [478/483]	0.24
Normalised Haemoglobin (Z–score)	-2.4 (2.1) [334/340]	-2.6 (2.0) [138/139]	-2.4 (2.1) [476/483]	0.19
White Cells ($\times 10^9$/L)	14.3 (11.0–17.6) [338/340]	13.6 (9.4–18.1) [138/139]	14.1 (10.8–17.9) [480/483]	0.47
Neutrophils ($\times 10^9$/L)	8.9 (6.7–12.4) [333/340]	9.5 (6.0–12.3) [137/139]	9.0 (6.5–12.3) [474/483]	0.93
Neutrophils (%)	67 (55–76) [333/340]	70 (59–78) [137/139]	68 (56–77) [474/483]	0.042
Platelets ($\times 10^9$/L)	374 (292–478) [337/340]	319 (239–426) [133/139]	358 (277–458) [474/483]	<0.001
ESR (mm/Hr)	74 (45–100) [268/340]	66 (44–90) [108/139]	70 (44–95) [379/483]	0.13
CRP (mg/L)	95 (53–151) [333/340]	133 (75–209) [133/139]	104 (59–167) [470/483]	<0.001
AST (U/L)	36 (26–50) [162/340]	34 (25–59) [70/139]	36 (26–51) [233/483]	0.82
ALT (U/L)	29 (16–72) [320/340]	33 (20–69) [129/139]	30 (17–70) [453/483]	0.25
Albumin (g/L)	34 (30–37) [318/340]	30 (26–35) [128/139]	33 (28–36) [450/483]	<0.001
Bilirubin (μmol/L)	6 (4–9) [318/340]	6 (4–10) [128/139]	6 (4–10) [450/483]	0.75
Treatment Modalities				
IVIG	**340/340 (100.0%)**	**139/139 (100%)**	**479/483 (99%)**	
1 (g/kg)	10/326 (3.1%)	5/134 (4%)	15/460 (3%)	0.92
2 (g/kg)	305/326 (93.6%)	124/134 (93%)	429/460 (93%)	
Other dose	11/326 (3.4%)	5/134 (4%)	16/460 (4%)	
Unknown	14/340 (4.1%)	5/139 (4%)	19/479 (4%)	
Days from fever onset to IVIG	7 (5–9)	6 (5–7)	6 (5–8)	<0.001
Aspirin	**287/322 (89.1%)**	**109/133 (82%)**	**399/459 (87%)**	**0.010**
3–5 (mg/kg/day)	5/322 (1.6%)	10/133 (8%)	15/459 (3%)	
30–50 (mg/kg/day)	1/322 (0.3%)	0/133 (0%)	1/459 (0%)	
80–100 (mg/kg/day)	29/322 (9.0%)	14/133 (11%)	44/459 (10%)	
Other dose	10/332 (3.0%)	1/134 (1%)	11/470 (2%)	
Unknown	28/340 (8.2%)	24/139 (17%)	52/483 (11%)	
Corticosteroids	**17/28 (60.7%)**	**9/24 (38%)**	**26/52 (50%)**	**0.23**
Oral only	6/28 (21.4%)	7/24 (29%)	13/52 (25%)	
Intravenous only	5/28 (17.9%)	8/24 (33%)	13/52 (25%)	

'Treatment Response' was determined by the administration of a second round of treatment due to perceived failure to respond to an initial dose of IVIG. Only children who received at least one dose of IVIG are included in the 'Treatment Response' columns, whereas all children are included in the 'All' column. A dose may be listed as Unknown if it was not possible to calculate the dose/kg. Laboratory results are from blood samples taken prior to the administration of IVIG. Haemoglobin is presented as raw data and age–normalised data; normalised haemoglobin is based on normative data as published in the Harriet Lane Handbook, 22nd Edition (see Supplementary Methods). Categorical data are summarised as frequency (%) and compared using Pearson's $\chi 2$ statistic. Continuous data are summarised as median (interquartile range) and compared using the Kruskal–Wallis test, except for the age–normalised haemoglobin, which is summarised as mean (standard deviation) and compared using ANOVA. ALT, alanine transaminase; AST, aspartate transaminase; CRP, C–reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate. GP, general practitioner; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Supplementary Table 6.6: Multivariable Logistic Regression Model of Non-Response to Intravenous Immunoglobulin as Primary Therapy for Kawasaki Disease

Predictor	OR	95% CI	*P*	Pseudo-R^2
Age (years)	1.07	0.99–1.16	0.08	0.026
Sex	1.03	0.68–1.56	0.88	
Number of cardinal clinical features	0.94	0.77–1.14	0.51	
Days from fever onset to IVIG	0.88	0.82–0.95	0.002	

The pseudo-R2 was 0.026 and was higher for each predictor removed from the model. CI, confidence interval; OR, odds ratio.

Supplementary Table 6.7: Agents Used as Secondary Therapy for Children Diagnosed with Kawasaki Disease

	Non-Responders
Received Second Dose IVIG	**123/139 (88.5%)**
IVIG Dose (g/kg)	
1	4/118 (3.4%)
2	110/118 (93.2%)
Other dose	4/118 (3.4%)
Received Corticosteroids	**44/139 (31.7%)**
Corticosteroid Route:	
Oral only	9/44 (20.5%)
Intravenous only	19/44 (43.2%)
Oral and Intravenous	16/44 (36.4%)
Received Infliximab	**6/139 (4.3%)**

Data are summarized as frequency (%). IVIG, intravenous immunoglobulin.

Supplementary Table 6.8: Clinical Outcomes of Children Diagnosed with Kawasaki Disease, by Response to Therapy

	Treatment Response		All	
	Responders	**Non-Responders**		***P***
	N = 340	**N = 139**	**N = 483**	
Admission Outcomes				
Admitted to ICU/HDU	9/340 (2.7%)	16/139 (12%)	25/483 (5.2%)	<0.001
Respiratory Support	2/9 (22%)	7/16 (44%)	9/25 (36%)	0.282
Blood Pressure Support	4/9 (44%)	7/16 (44%)	11/25 (44%)	0.973
ECMO	0/9 (0%)	1/16 (6%)	1/25 (4%)	0.444
Total admitted days	3.5 (3–5)	6 (4–10)	4 (3–6)	0.001
Acute Coronary Artery Outcomes				
Inpatient Echocardiogram	265/332 (79.8%)	128/139 (92.1%)	397/475 (83.6%)	0.001
Fever Onset to Echocardiogram (days)	8 (6–10)	7 (5.5–10)	8 (6–10)	0.299
Worst Coronary Artery Z–score				
<2	154/238 (64.7%)	70/111 (63%)	227/353 (64.3%)	0.451
2 to <2.5	23/238 (9.7%)	10/111 (9%)	34/353 (9.6%)	
2.5 to <5	45/238 (18.9%)	24/111 (22%)	69/353 (19.6%)	
5 to <10	13/238 (5.5%)	3/111 (3%)	16/353 (4.5%)	
≥10	3/238 (1.3%)	4/111 (4%)	7/353 (2.0%)	
Subacute Coronary Artery Outcomes				
Follow–Up Echocardiogram	258/325 (79.4%)	122/137 (89.1%)	383/466 (82.2%)	0.013
Discharge to Echocardiogram (weeks)	6 (5–8)	6 (59)	6 (5–8)	0.233
Worst Coronary Artery Z–score				
<2	182/225 (80.9%)	79/103 (77%)	264/331 (79.8%)	0.286
2 to <2.5	17/225 (7.6%)	7/103 (7%)	24/331 (7.3%)	
2.5 to <5	17/225 (7.6%)	10/103 (10%)	27/331 (8.2%)	
5 to <10	5/225 (2.2%)	1/103 (1%)	6/331 (1.8%)	
≥10	4/225 (1.8%)	6/103 (6%)	10/331 (3.0%)	

Wherever possible coronary artery Z-scores were re-calculated using the method of Dallaire & Dahdah (Dallaire F, Dahdah N. New Equations and a Critical Appraisal of Coronary Artery Z Scores in Healthy Children. Journal of the American Society of Echocardiography. 2011 Jan;24(1):60–74); where this was not possible, but a Z-score had been documented, the documented Z-score was used. Categorical data are summarised as frequency (%) and compared using Pearson's χ^2 statistic. Continuous data are summarised as median (interquartile range) and compared using the Kruskal-Wallis test. ECMO, extracorporeal membrane oxygenation; ICU/HDU, intensive care unit / high dependency unit.

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Chapter 7: Conclusions

In the introduction to this thesis I outlined two broad areas fields of inquiry that guided the subsequent research. These were:

> *What is the epidemiology of Kawasaki disease (KD) in Australia?*
> *How do clinicians approach the management of KD in Australia?*

In Part One these questions were explored in two reviews, highlighting specific points of uncertainty or contention. With regard to epidemiology, evidence from around the world of increasing incidence and seasonal variation was reviewed, with gaps in local understanding identified. The challenge of case definition — and implications for comparisons between studies — was also discussed at length. Three specific research questions where then articulated:

1. *What is the current incidence of KD in Australia?*
2. *Is there evidence of increasing incidence of KD in Australia?*
3. *Is there evidence of seasonal variation of KD in Australia?*

These questions were addressed in the study presented in Chapter 4. To address the challenges associated with case definition I used two independent national datasets. The first was the *National Hospital Morbidity Database* (NHMD); the NHMD is maintained by the Australian Institute of Health and Welfare and records hospitalisations,[1] from which it was possible to calculate the hospitalisation rates over a 25-year period. As noted in Chapter One, hospitalisation rate overestimates KD incidence as children can have multiple admissions within an episode of KD. I sought to address this issue by comparing the hospitalisation rate to the treatment rate, derived from the second dataset.

The second dataset was the Supply *Tracking Analysis Reporting System* (STARS), maintained by the Australian Red Cross Lifeblood. STARS records the allocation of intravenous immunoglobulin (IVIG); patient details for each dose of IVIG were available, making it possible to account for children who had received multiple doses within an episode of KD. I hypothesised that the treatment rate would more accurately correlate with the true diagnosis rate. This was supported by results from to other studies (presented in Chapter Three and Chapter Six), which showed very high rates of IVIG use for the treatment of KD.

The average annualised treatment rate over the period during which the datasets overlapped was 14.31 per 100,000 children under 5 (95% confidence interval 13.67–14.97); I believe that this is likely to represent the most accurate estimate of KD incidence in Australia. Pleasingly, the average annualised hospitalisation rate over the same period was very similar, at 14.99 per 100,000

children under 5 (95% CI 14.33–15.66). I therefore felt more confident proceeding with an analysis of hospitalisation data, which extended over 25 years.

Over a 25-year period the KD hospitalisation rate in Australia increased from 9.39 per 100,000 children under 5 (1993–97, 95% CI 8.66–10.16) to 17.51 per 100,000 children under 5 (2013–17, 95% CI 16.59–18.47), for a mean annual increase of 3.5% (95% CI 2.9–4.1). Interestingly, all of that increase occurred among children between 1 and 4 years of age, with hospitalisations among children under 1 year changing very little over the period.

Finally, the resolution (both spatial and temporal) of the STARS dataset permitted an analysis for evidence of seasonal variation in rate of KD. I found evidence of a small seasonal effect on KD treatment rates, with slightly more cases in July to December as compared with January to June. On regional analysis this effect was not seen in more northern states, however case numbers from those jurisdictions were small.

In summary, I derived the most reliable estimate of KD incidence in Australia by combining datasets with different inherent biases. I observed increasing incidence over a 25-year period, concurrent with a changing age distribution. Finally, I reported the first evidence of seasonal variation in KD rates from Australia.

The review of KD management in Chapter Two identified a number of important areas characterised by a lack of evidence, a lack of consensus, or a divergence of consensus from evidence. Some of these included:

> *1. The approach to immunisation with live vaccines after treatment with IVIG.*
> *2. The role of aspirin in the acute phase of KD, with particular attention to dose.*
> *3. The role of corticosteroids in the management of KD.*
> *4. The definition and treatment of "IVIG resistant" KD.*

The first of these was addressed in a stand-alone study, presented in Chapter Five. Australian guidelines align with those from North America, recommending that live vaccines be postponed for 11 months after receiving IVIG.[11–13] In a retrospective audit of immunisation practices after IVIG for KD at two specialist children's hospitals in Sydney, I observed that these recommendations are frequently not followed. Indeed, more than half of the children who received IVIG in the 11 months prior to a scheduled live vaccine went on to receive that vaccine in breach of the recommendations. I argued that this was likely due to under recognition of the issue and poorly integrated care between providers. In reviewing the literature that informed the

recommendations I also highlighted significant deficits in knowledge, noting that the 11-month postponement interval had been derived by extrapolation from low-quality data.[14] In lieu of more robust data I sought to re-emphasize attendance to and maintenance of the public health systems that ensure high rates of effective immunisation.

My analysis of Australian responses to an international survey about the management of KD (presented in Chapter Three) highlighted significant variation in practice with regard to the first three points. Australian guidelines are notable for recommending that low-dose aspirin be initiated at diagnosis[2,3]; this is in contrast to medium- or high-dose aspirin recommended elsewhere.[4–6] The reported practice of Australian clinicians (as observed in their responses to the KD survey) was highly variable, with no consensus around a preferred dose. Actual practice, observed in the prospective cohort study presented in Chapter Six) was very different — 86.9% of patients only ever received low-dose aspirin. This may indicate evolving practice as clinicians become more comfortable with a low-dose only approach. As discussed in Chapter Two, neither medium-dose nor or high-dose aspirin have been shown to be superior to low-dose or no aspirin during the acute phase of KD.[7–9] I argue that current Australian practice is best aligned with the available evidence, and hope that recognition of the successful use of this approach in Australia might aid progressive reform in this aspect of KD management globally.

I observed a clear difference between responses by generalist and specialist clinicians with regard to the reported use of corticosteroids for the management of KD — specialists were more likely than generalists to prescribe corticosteroids for both primary adjunctive therapy and for the treatment of IVIG resistant disease. The rate of corticosteroid use observed in the prospective cohort study was closer to that reported by specialist clinicians, which likely reflects recruitment from specialist referral hospitals. It is increasingly recognised that corticosteroids do have a role in the management of KD,[10] however heterogeneity in study design to date makes the interpretation of results challenging.

Most Australian respondents to the KD survey indicated that they would diagnose IVIG resistance if there was persistent or recrudescent fever 24 hours after the end of the IVIG infusion. This is earlier than recommended in most guidelines (typically 36–48 hours[4–6]) and was earlier, on average, than responses to that survey by New Zealand clinicians. Data from the prospective cohort study supported this finding, with most cases of IVIG resistance diagnosed less than 36 hours after the end of the IVIG infusion. That cohort had a comparatively high overall rate of IVIG resistance (29%), which may reflect overdiagnosis due to premature attribution of fever to treatment

failure. Current recommendations are based on consensus opinion[4,6]; in the absence of a relevant evidence base there is a clear need for global collaboration around an agreed definition of IVIG resistance. This would not only support enhanced patient care, but would aid research that uses treatment failure as a key outcome.

Finally, one key finding from the prospective cohort study in Chapter Six related neither to epidemiology nor management, but to diagnosis: 23.6% of children treated for KD did not fulfil even the most permissive diagnostic criteria outlined in the most recent statement by the American Heart Association.[4] This important finding — though unexpected — highlights the strength of the study model, which enrolled cases based on 'clinician diagnosis' rather than using a case definition. Those with what I called 'Uncertain KD' differed little from those with Complete or Incomplete KD at presentation, yet the incidence and severity of coronary abnormalities in that group were much lower. More than fifty years after Dr Kawasaki's seminal monograph on what he called mucocutaneous lymph node syndrome the entity now named in his honour is still defined by the clinical features that he observed. This has the effect of rendering important questions difficult to articulate: Did any of the children who failed to meet diagnostic criteria for KD have KD? Did all of the children with complete KD have the same disease process? These are questions of ontology: outside the scope of this thesis, yet fundamental to its subject; I return to them in the *Postscript*. Putting ontological uncertainties to one side; the rarity of adverse coronary outcomes in children who do not meet the diagnostic criteria for KD should embolden clinicians to adhere to those criteria in the face of diagnostic uncertainty. The majority of those with Uncertain KD received IVIG on or before day five of fever; a watchful waiting approach may help reduce rates of overdiagnosis and associated resource overuse.

Implications for Policy, Practice, & Research

This work was funded by the *National Blood Authority*, which oversees the provision of publicly funded blood products in Australia. The appropriate use of a scare resource (IVIG) is obviously of great interest. My research has demonstrated that Australian clinicians largely prescribe IVIG for KD in accordance with international best practice. There are two areas of possible overuse: Firstly, the observation that a significant subset of children was diagnosed and treated for KD without fulfilling diagnostic criteria may indicate an element of overdiagnosis and consequent overtreatment. Secondly, the relatively high rate of retreatment (which may represent premature diagnosis of IVIG resistance) might also represent overuse. I do not believe, however, that efforts on these points are likely to result in significant dividends for resource stewardship. Firstly, any overuse in these areas is likely to be only marginal in the context of IVIG used for KD in Australia. I have

suggested that clinicians take a watchful-waiting approach in cases where the diagnosis of KD is suggested before diagnostic criteria are met. It is possible that most children so managed would still be diagnosed with — and treated for — KD, only slightly later. Secondly, children with KD represent a tiny fraction of the demand for immunoglobulin products in Australia (about 0.3%, as discussed in Chapter Two).

While these issues may be marginal at a population level, the impact at a patient level can be significant. Each decision to administer IVIG for the management of KD represents a calculus weighing possible benefits against possible risks. Children who receive IVIG in the context of an incorrect KD diagnosis are exposed to the same risks without any clear benefit. Recommendations about the diagnosis of KD, and of IVIG resistance, are based on consensus agreement of relevant experts. The observation that real-world practice frequently differs from these recommendations is indicative of a state of clinical equipoise; large, prospective studies — whether observational or interventional — that can inform future recommendations around treatment thresholds should be pursued. Such efforts would be greatly aided by coordinated international collaborations that capitalise on existing practice variation.

Finally, I propose that there is a need for the KD research community to revisit fundamental questions around the nature of KD. In the *Postscript* that follows I will seek to highlight some of the ways in which the current paradigm is unsuited to addressing priority topics in KD research. I critique the current syndrome-centred paradigm on the grounds of historical accuracy and ontological precision; I then submit an alternative, process-centred paradigm for consideration and comment.

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Chapter 8: Postscript—The Kawasaki Disease Paradigm

Introduction

> *Kawasaki disease is an acute vasculitis of childhood that leads to coronary artery aneurysms in ≈25% of untreated cases.*[1]

So begins the 2017 Scientific Statement for Health Professionals from the American Heart Association on the Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease. The line makes several ontological* claims about Kawasaki disease (KD), namely:

1. That KD is a disease entity†. This claim is implied by the following:
2. That among disease entities, KD is of the *kind* 'vasculitis'.
3. That the set of all patients with KD contains a subset (25%) in whom coronary artery aneurysms are a consequence (in untreated cases).

These claims are axiomatic to what has been called the *Kawasaki Disease Paradigm*.[5] The preceding thesis, and the epidemiological studies, interventional trials, and clinical practice guidelines discussed therein, exist within that paradigm. In this critical essay I will highlight logical and linguistic deficiencies of that paradigm and present an alternative paradigm for consideration.

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* Ontology is the philosophical study of being. It seeks to classify—in a definitive and exhaustive fashion—entities in all spheres of being. It asks questions like "What kinds of things exist?", "To what classes do things belong?", and "How do these classes relate?"[2]

† The term *disease entity* has a special meaning within realist medical ontology. A disease entity is a *dependent continuant* that exists is reality.[3] *Continuants* exist at a moment in time and continue to exist through time, like a person. In contrast, *occurrents* have temporal parts, like the life of a person. *Independent continuants* can exist independently (e.g., a person), whereas *dependent continuants* can only exist by virtue of another entity (e.g., a rash). The concept of continuants and occurrents is described clearly in chapter 14 of *Artificial Intelligence: Foundations of Computational Agents, 2nd edition*. Cambridge University Press, 2017 (available at: https://artint.info/2e/html/ArtInt2e.Ch14.S3.SS3.html).
In discussing the levels of abstraction relevant to ontology, Smith and Ceusters outline three levels: 1, the level of reality; 2, the level of cognitive representations of this reality; and 3, the level of textual and graphical artifacts.[4] Disease entities (in the realist worldview) exists in the *real world*—i.e., at the level of reality L1.[3]

Contested History of "Kawasaki Disease"

In January 1961 Dr Tomisaku Kawasaki—then a paediatrician at Japan Red Cross Central Hospital—reviewed a four-year-old boy who presented with persistent fever for two weeks, with inflamed mucous membranes, cervical lymphadenopathy, and erythematous rash. After considering a range of differential diagnoses (including measles, scarlet fever, and Stevens-Johnson syndrome) Kawasaki discharged the boy without assigning a diagnosis (labelling the case 'diagnosis unknown').[6] Three years later Kawasaki presented a series of 20 similar patients, identifying them as instances of mucocutaneous ocular syndrome (MCOS)—an entity already described in children by paediatricians Dr Itoga and Dr Yamagishi in 1960.[7]

"Mucocutaneous Lymph Node Syndrome"

By 1967 Kawasaki had amassed a cohort of 50 cases, which he described in the Japanese journal *Arerugi*.[8] The monograph was meticulous, with charts of body temperature and clinical signs reproduced for each child by hand, as well as photographs of clinical signs and photomicrographs of pathological specimens of skin and lymph nodes. All cases had fever for at least 6 days and the vast majority had conjunctival congestion, oro-mucosal inflammation, and an erythematous rash that involved the acral surfaces with subsequent desquamation. Just over half of the cases were under the age of two years.

Kawasaki discussed possible infectious and non-infectious causes, rejecting each in turn, before turning his attention to MCOS. Tracing the historical use of the term to at least the 1940s, he made the ontological critique that MCOS subsumed multiple discrete clinical entities (Reiter disease, Behçet's disease, and 'multiform exudative erythema syndrome'), and thus was not itself a coherent and distinct entity. Turning to the age distribution he noted that few infantile cases had been described, with Itoga and Yamagishi's the only series in which most cases were under the age of two years. Finally, he contrasted the clinical features of his cohort with those described by Itoga and Yamagashi. The latter had observed generalised desquamation and blisters whereas Kawasaki observed periungual desquamation and no blisters; subtle differences in the ocular, mucosal, and lymphatic signs were also outlined. He concluded that the entity he presented was distinct, and proposed the name Acute Febrile Muco-Cutaneous Lymph Node Syndrome (MCLS*).[8]

In the description of MCLS in his *Arerugi* paper, Kawasaki stated that "...patients spontaneously recover without any sequelae".[8] Evidence to the contrary soon began to accumulate. Nation-wide surveys of the condition in Japan reported a case fatality rate of 1.7%, with sudden death occurring in the

* This is variably referred to as MCLS, acute MCLS, and AMCLNS. The former will be used in this essay.

context of acute cardiac failure.[9] Post-mortem examinations demonstrated sequelae of vasculitis, with the formation of aneurysms in the coronary arteries of many fatal cases[10,11]; angiograms demonstrated clinically inapparent aneurysms in children who survived.[12] A large, single-centre cohort study reported that approximately 25% of untreated patients would have coronary aneurysms in the subacute phase of the illness, of which about half persisted after one year.[13*]

The histopathology of coronary lesions associated with MCLS was described by Fujiwara and Hamashima in 1978.[10] They presented the autopsy findings of 20 children who had died from MCLS in Japan, with the time from illness onset to death ranging from 9 days to 4½ years. The child who died at day 9 of illness had no coronary aneurysms, however microvessels and small coronary branches had evidence of both endarteritis (inflammation of the vessel wall) and periarteritis (inflammation of the adventitia); no inflammatory changes were seen in the tunica media. As the time from illness onset to death increased inflammation was increasingly observed in larger arteries, involving the tunica media (described as panarteritis). A diverse range of infiltrating cells (including neutrophils and lymphocytes) was noted, sometimes leading to necrosis of the media.[†]

"Infantile Periarteritis Nodosa"

The coronary pathology of MCLS shared a striking resemblance to that of infantile periarteritis[‡] nodosa (IPN), an entity that had been described in post-mortem reports from at least the 1870s.[26–28] The apparent association was one

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[*] This study, which at the time of writing has been cited over 1,600 times, seems largely responsible for this frequently-cited statistic.[1,14] Suzuki *et al* identified aneurysms in only 93 out of 1,100 (8.5%) of children with KD, but at significantly later follow-up (median 4 years 7 months).[15] The few studies of the incidence of coronary artery aneurysms in KD that have been performed in non-Japanese populations prior to the use of IVIG have been comparatively small. The reported incidence of aneurysms has ranged from 8% in the UK[16] to between 14% and 25% in the USA.[17–20]

[†] A later study of both autopsy and heart transplant cases would identify three distinct pathological processes in the coronary arteries of children with severe KD.[21] Necrotising arteritis (NA) of medium-sized muscular arteries was observed early in the disease process. It proceeds from the lumen outwards, with neutrophilic invasion and the sequential destruction of the intima, internal elastic lamina, tunica media, and external elastic lamina—sometimes extending to the adventitia. This was followed by an overlapping subacute/chronic (SA/C) vasculitis of both muscular and elastic arteries; lymphocytic invasion was predominant with few neutrophils seen. Both necrotising arteritis and subacute/chronic vasculitis demonstrated destruction of the vessel wall and the development of aneurysms. Finally, a delayed stenosing process (luminal myofibroblastic proliferation, LMP) was observed—seemingly related to SA/C vasculitis.

[‡] The terms *periarteritis* and *polyarteritis* are used interchangeably in the literature.[22–25] The former is used henceforth to emphasize its distinction from classical polyarteritis nodosa.

that Kawasaki actively opposed.[26] In an article published in *Pediatrics* in 1974 he noted the similarities but opined that "...description of the clinical features of [infantile periarteritis nodosa] is insufficient in the literature." That statement was disingenuous; among the articles cited in that paper was a case report by Canadian pathologist Dr Munro-Faure describing a fatal case of infantile periarteritis nodosa in a 3-month-old boy who fulfilled what would later be the diagnostic criteria for complete KD.[29] Autopsy revealed multiple aneurysms of the coronary arteries characterised by necrotising arteritis extending from the intima to the adventitia with destruction of the internal elastic lamina and tunica media. Munro-Faure cited case reports of 18 other cases, many of which would today be identified as KD.[*]

Indeed, throughout the 1970s the relation of these entities was actively discussed. In a letter in *The Lancet* in 1976, Dutch cardiac pathologist Dr Becker argued that there was no reason to conclude that the two entities were discrete.[30] This was followed by a post-mortem study by American pathologists Landing and Larson, published in *Pediatrics* in 1977. They compared clinical and post-mortem pathological findings from 20 children with IPN, two with MCLS, and three with classical polyarteritis nodosa. They concluded that IPN and fatal MCLS were indistinguishable (and distinct from classical polyarteritis nodosa), and recommended that IPN and MCLS be consolidated under a single term[†].[34] Indeed, this appears to have occurred: Medline lists only 8 manuscripts published in the years after 1977 that refer to IPN but not to MCLS/KD.

"Kawasaki Disease"

The label MCLS was in wide use in both the Japanese and English literature in the 1970s. The change to "Kawasaki Disease" can be pinpointed to 1976: first with its adoption by the Japanese MCLS research group,[35] followed in English in an editorial in *The Lancet*.[36] Although not without controversy,[31,32] the new name was quickly adopted around the world. In support of the adoption of the *Kawasaki* eponym Landing and Larson pointed to the recognition of the "...great contribution of Japanese workers".[34] This suggests a narrative of consensus under the leadership of one individual, yet the reality was far more complex.[26] Kawasaki was not the first in Japan to note the clinical picture that he called MCLS, nor was his conception of the underlying process the most

[*] A strikingly similar case was described by Sinclair and Nitsch in 1949.[25]

[†] They suggested either the label MCLS or Kawasaki disease. This treats the terms *syndrome* and *disease* as synonyms, which they are not.[26,31,32] *The Oxford Concise Medical Dictionary* lists only one definition for syndrome ("a combination of signs and/or symptoms that forms a distinct clinical picture indicative of a particular disorder") but two definitions for *disease* (the general "any bodily abnormality or failure to function properly, except that resulting directly from physical injury", and the more specific "disorder with a specific cause (which may or may not be known) and recognizable signs and symptoms").[33]

complete (he actively opposed the recognition of coronary complications advocated by his peers[*]).[26]

The adoption of the descriptor *disease* was both more complex and more controversial. The Japanese term *byō* (病, a somewhat vague term meaning "ill" or "sick"[39]) was chosen over the more technical *shōkōgun* (症候, meaning "syndrome"[39]) for the condition's Japanese name *Kawasakibyō* (川崎病), as it was thought to be more appropriate for communication with families.[26] The adoption of *disease* in English had a different motivation. In English the word *disease* has a general meaning ("any bodily abnormality or failure to function properly, except that resulting directly from physical injury"[33]) and a more technical meaning ("disorder with a specific cause [which may or may not be known] and recognizable signs and symptoms"[33]). Kushner *et al* (in their exhaustive historical analysis of the Kawasaki disease paradigm) describe the adoption of the term *Kawasaki disease* by the CDC; they note that the latter, technical definition that was specifically invoked as a rhetoric response to prevalent scepticism regarding the status of MCLS as a discrete entity[26†]

Table 8.1: Kawasaki Disease, Kawasaki Syndrome, or Mucocutaneous Lymph Node Syndrome—Use in the Academic Literature by Decade

	1970s	1980s	1990s	2000s	2010s	2020s
Kawasaki Disease	7[‡][10,42–47]	14[15,48–60]	18[13,61–77]	17[14,78–93]	19[1,21,90,94–109]	20[110–129]
Kawasaki Syndrome	0	6[17,130–134]	2[135,136]	3[137–139]	1[140]	0
Mucocutaneous Lymph Node Syndrome	13[9,12,34,41,141–149]	0	0	0	0	0

Condition labels used in the titles of the 20 most highly-cited papers in the English-language literature by decade. The label *Mucocutaneous Lymph Node Syndrome* includes *acute mucocutaneous lymph node syndrome* and *acute febrile mucocutaneous lymph node syndrome*.

The term *Kawasaki disease* remained controversial—Kawasaki himself preferred the term *syndrome*.[26] Indeed, *Kawasaki syndrome* persisted alongside *Kawasaki disease* for some time, and is still occasionally encountered.[31,40] While some authors have sought to defend the distinction,[31,32] the common use of the terms gives the impression that they are interchangeable (an important point to which I will return). The overarching trend has been a consolidation of disparate terms under the now-dominant *Kawasaki disease*. Of the twenty most highly cited academic papers published on the topic in the English-language literature in the 1970s only 35% used the

[*] Dr Takajiro Yamamoto had been collating a case series similar to Kawasaki's during the 1950's and 60's, but with an emphasis on cardiac associations.[26] Dr Noboru Tanaka had documented sudden cardiac death in a child diagnosed with MCLS by Kawasaki in 1965[27,37,38]; he continued to identify MCSL with IPN against Kawasaki's vocal opposition.[26]

[†] The reader is strongly encouraged to refer to Kushner *et al*[26] for the authoritative historical investigation of this event.

[‡] Not counted here is one manuscript entitled "Mucocutaneous Lymph Node Syndrome (Kawasaki Disease) in Adults"[41].

label *Kawasaki Disease*; the top 20 papers in the current decade to date have used that label exclusively (**Table 8.1**).

Incompleteness

By the early 1980s there was an emerging realisation that coronary pathology characteristic of KD could occur in children who did not fulfil the formal epidemiologic case definition.[150,151] Rowley *et al* presented a series of four cases of coronary artery aneurysms in children with so-called 'incomplete' KD, and reviewed the case literature of the phenomenon.[48] They highlighted the importance of recognising peripheral desquamation as a delayed sign of KD, and suggested that the diagnosis be considered "...in an infant or child with a prolonged unexplained febrile illness".

The issue was formally addressed in diagnostic recommendations two years later in a consensus statement representing the North American attendees of the Third International Kawasaki Disease Symposium.[152] The statement distinguished those children with sufficient clinical signs but fewer than five days of fever (in whom "...some believe..." the diagnosis of KD could be made by experienced individuals) from those without sufficient clinical signs (described as 'atypical' or 'incomplete'[*]). The authors identified that infants (under 12 months) were at particular risk for this presentation and encouraged the reader to remain vigilant in that age group—observing for associated features, such as thrombocytosis, arthritis, anterior uveitis, and sterile pyuria.

The most recent statement from the American Heart Association (AHA) sought to provide clearer advice around the diagnosis of incomplete KD. The authors proposed a diagnostic algorithm for incomplete KD, acknowledging that in the absence of a 'gold standard' for diagnosis "...[the] algorithm cannot be evidence based but rather represents the informed opinion of the expert committee".[1] The algorithm outlines an approach to children with two or three cardinal clinical signs of KD and at least five days of fever, or infants with unexplained fever for at least seven days. For children with raised inflammatory markers[†] treatment with IVIG is recommended if there is

[*] Both terms are still encountered[1] with reference to children who do not fulfil sufficient clinical criteria for a diagnosis of complete KD, however 'incomplete' is preferred. The 2004 American Heart Association statement recommended that 'atypical' be reserved "...for patients who have a problem, such as renal impairment, that generally is not seen in Kawasaki disease".[14]

[†] Defined as a C-reactive protein concentration ≥30 mg/L or an erythrocyte sedimentation rate ≥40 mm/hr.

derangement of specified laboratory markers[*] or echocardiographic evidence[†] of coronary abnormalities consistent with KD.[1]

While the clinical presentation of 'incomplete KD' can be less dramatic than complete KD, it is clear that the severity of observable clinical signs does not correlate with the likelihood or severity of adverse coronary outcomes[153,154]—as stated by Sonobe *et al*, incomplete KD "...should not be equated with mild KD".[153] To the contrary: the incidence of adverse coronary outcomes appears to be higher among children with incomplete KD.[153] This additional risk is likely the result of multiple overlapping factors, such as delayed diagnosis and a slightly younger age profile (incomplete KD is more commonly observed in children under 1 year of age, which also appears to confer additional risk of aneurysm formation).[154] Manlhiot *et al* found no significant demographic, clinical, or laboratory differences between children with incomplete versus complete KD, concluding that the entities are "two sides of the same coin".[155] The distinction between complete and incomplete KD therefore appears to be semantic, rather than ontological; an artifact of a paradigm that defines the disease entity by one of its clinical syndromes.

Global (Re)Emergence

Following the publication of Kawasaki's initial case series, in 1970 the Japanese government funded the establishment of what would become the Kawasaki Disease Research Committee. The committee produced and distributed diagnostic guidelines and conducted epidemiological surveys approximately every two years.[‡] Surveys conducted through the 1970s consistently reported increasing case numbers, however the number of participating hospitals increased from 1,452 to 1,688 over that decade. On a background of apparent rising incidence the surveys also identified three nation-wide epidemics (in 1979, 1982, and 1986). By the early 2000s the incidence of KD among children under the age of 5 years in Japan exceeded 150 per 100,000 per year.

Throughout the 1970s MCLS/KD was also starting to be reported outside of Japan: first in Korea (1973[156]), then Hawaii (1974[157]), Greece (1975[158]), Canada (1975[159]), the continental United States (1975[160]), The Netherlands (1976[28]), Australia (1976[42]), West Germany (1977[161]), Italy (1977[162]), Belgium (1977[163]), Sweden (1977[23]), England (1977[164]), Scotland (1977[22]), Turkey (1977[165]), and

[*] These include: anaemia (age corrected), thrombocytopaenia (after the 7th day of fever), hypoalbuminaemia, elevated alanine aminotransferase, leucocytosis, and pyuria.

[†] These include: specified coronary abnormalities, decrease left ventricular function, mitral valve incompetence, and pericardial effusion.

[‡] Surveys were sent to every hospital with more than 100 beds and a paediatric department; later, specialist paediatric hospitals with fewer than 100 beds were also included.[11]

Kuwait (1978[166]). KD has now been reported from most countries around the world.[167]

As already discussed, IPN likely represents the pathological diagnosis given to fatal cases of what we now call KD. The extensive case literature of IPN in America and Europe going back to the 1870s[*] therefore suggests that the entity we now call KD existed outside of Japan prior to 1967.[26,168,169] The possible implications of this have been pursued by Kushner and Abramowsky to suggest a fascinating hypothesis as to the provenance and global spread of IPN/MCLS/KD. Noting the long case history of IPN in America, they proposed that the epidemics of KD in Japan in the 1970s represented the consequence of a novel agent having been introduced into a naïve population during the post-war years.[169] They cited a large retrospective review of medical records at Tokyo University Hospital from 1940 to 1965, which found no cases suggestive of KD from 1940–49 but ten cases from 1950–65.[170] This is in stark contrast to the traditional narrative that describes the global emergence of KD from Japan but which fails to account for Japan's unique[†] explosion in incidence.[171]

An Incoherent Paradigm

The *Kawasaki Disease Paradigm* suggests that there exists a disease entity characterised by a constellation of cardinal clinical signs, of which a subset of afflicted individuals develop coronary artery aneurysms. The centrality of the clinical syndrome is cemented by the eponymous attribution—when we speak of Kawasaki disease we are talking about that entity described by Dr Kawasaki—even as the diagnostic criteria have shifted to capture instances of sequelae that he did not recognise. I will argue that the *Kawasaki Disease Paradigm* maps poorly onto the history and clinical spectrum of the entity that causes coronary artery aneurysms in infants and children.

The Importance of Nomenclature

Many of the conceptual forms and ontological assumptions that I seek to critique are enforced by the semantic and syntactic structures of the paradigm, from which they naturally arose. This constrains the field of critique as certain questions are rendered semantically complicated, if not incoherent. I will

[*] Much has been written about the history of IPN/MCLS/KD in Europe and America, however the Australian experience has been neglected. Dr Terry Schultz, a pathologist from the rural town of Wangaratta in Victoria, described a case in 1989 of a 34-year-old man who died suddenly after a run. Autopsy revealed multiple calcified coronary artery aneurysms without significant atheroma in the unaffected coronary segments or the aorta. The only time that the man had ever been unwell was as an infant, when he was admitted to hospital for what was then labelled as glandular fever. This suggests the possibility that IPN/MCLS/KD existed in Australia at least 30 years previously (around 1967).

[†] The dramatic emergence of KD in Japan has been matched only in Hawaii.[169]

therefore propose an alternative paradigm—not least to assemble a linguistic toolkit more conducive to ontological precision.

Central to the paradigm is the name: *Kawasaki disease*. In the preceding pages I outlined the history of the Kawasaki disease label as it came to dominate over competing forms (such as *mucocutaneous lymph node syndrome* and *Kawasaki syndrome*). Two processes seem to have been at play in rendering *Kawasaki disease* the dominant label for the disease entity: substitution and equivalence[*]. Substitution, whereby the *Kawasaki disease* label has come to be used in favour of alternatives, has already been highlighted in **Table 8.1**. Equivalence, whereby competing labels are treated as interchangeable, can be seen in the titles of academic papers such as "Mucocutaneous Lymph Node Syndrome (Kawasaki Disease) in Adults.[41] Equivalence can also be seen in published biomedical ontologies[†] (**Table 8.2**). These include the familiar *International Classification of Disease* and *SNOMED CT*, as well as the highly domain-specific—such as the *Cigarette Smoke Exposure Ontology*. **Table 8.2** also highlights the diverse (and, I contend, confused) approaches to categorising *Kawasaki disease* and related concepts.

[*] These terms are mine for the purpose of this discussion.

[†] Ontologies (distinct from the philosophical domain of ontology, described earlier) are important in the fields of computer science and informatics. They seek to represent, in a clearly-defined logical structure, the categories and relations between concepts in one, or multiple, domains of discourse.

Table 8.2: Categorisation of Kawasaki Disease and Related Concepts in Published Biomedical Ontologies

Ontology	Tree	Notes
Artificial Intelligence Rheumatology Consultant System Ontology[172]	Examiner's Diagnosis ↳ Kawasaki Disease	
Cell Cycle Ontology[173] and Gene Expression Ontology[174] and Regulation of Gene Expression Ontology[175] and Regulation of Transcription Ontology[176] and Homeostasis imbalance process ontology[177]	abstract entity ↳ attribute ⇣ ↳ realizable entity ⇣ ↳ capability ⇣ ↳ disposition ⇣ ↳ disease ⇣ ↳ Kawasaki disease	Synonyms: - KWD
Cigarette Smoke Exposure Ontology[178]	entity ↳ continuant ⇣ ↳ dependent_continuant ⇣ ↳ specifically_dependent_continuant ⇣ ↳ realizable_entity ⇣ ↳ disposition ⇣ ↳ Disease ⇣ ↳ Vascular Disorder ⇣ ↳ Non-Neoplastic Vascular Disorder ⇣ ↳ Vasculitis ⇣ ↳ Kawasaki Disease	Synonyms: - Mucocutaneous Lymph Node Syndrome

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
Computer Retrieval of Information on Scientific Projects Thesaurus[179]	disease/disorder ↳ cardiovascular disorder ⋮ ↳ blood vessel disorder ⋮ ⇣ ↳ vasculitis ⋮ ⇣ ↳ arteritis ⋮ ⇣ ↳ polyarteritis nodosa ⋮ ⇣ ↳ Goodpasture's syndrome ⋮ ↳ mucocutaneous lymph node syndrome ⋮ ↳ temporal arteritis ⋮ ↳ Wegener's granulomatosis ↳ skin disorder ⇣ ↳ mucocutaneous lymph node syndrome ↳ syndrome ⇣ ⋮ ↳ chronic fatigue syndrome ⋮ ↳ mucocutaneous lymph node syndrome ⇣	Synonyms: - Kawasaki disease
Dermatology Lexicon[180]	DermLex ↳ DermLex terms ⇣ ↳ DLP ENTRIES ⇣ ↳ VASCULAR ⇣ ↳ VASCULITIDES ⇣ ↳ MEDIUM VESSEL VASCULITIDES ⇣ ↳ KAWASAKI DISEASE	
Emergency Care Ontology[181]	entitée ↳ objet abstrait ⇣ ↳ objet intentionel ⇣ ↳ état interne ⇣ ↳ état pathologique ⇣ ↳ maladie par mécanisme ⇣ ↳ maladie inflammatoire ⇣ ↳ maladie inflammatoire localisee ⇣ ↳ artérite ⇣ ↳ syndrome de Kawasaki	Synonyms: - kawasaki - syndrome adéno-cutanéo-muqueux [Kawasaki]

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
Experimental Factor Ontology[182]	experimental factor ↳ material property ⇣ ↳ disposition ⇣ ↳ disease ⇣ ↳ cardiovascular disease ⁞ ↳ vascular disease ⁞ ⇣ ↳ vasculitis ⁞ ⇣ ↳ predominantly medium-vessel vasculitis ⁞ ⇣ ↳ mucocutaneous lymph node syndrome ⁞ ↳ primary central nervous system vasculitis ⁞ ↳ thromboangiitis obliterans ⁞ ↳ vasculitis due to ADA2 deficiency ↳ genetic disorder ⁞ ↳ mucocutaneous lymph node syndrome ↳ inflammatory disease ⇣ ↳ lymphadenitis ⇣ ↳ cat scratch disease ↳ Kimura disease ↳ mucocutaneous lymph node syndrome ↳ sialadenitis	Synonyms: - infantile polyarteritis nodosa - Kawasaki disease - acute febrile mucocutaneous lymph node syndrome [MCLS] - acute febrile mucocutaneous lymph node syndrome - Kawasaki's disease - acute febrile MCLS - Kawasaki syndrome - MLNS - mucocutaneous lymph node syndrome
Galen Ontology[183]	TopCategory ↳ DomainCategory ⇣ ↳ Phenomenon ⇣ ↳ GeneralisedProcess ⇣ ↳ SpecificProcess ⇣ ↳ BodyProcess ⇣ ↳ NAMEDNonNormalProcess ⇣ ↳ NAMEDPathologicalProcess ⇣ ↳ NAMEDSystemicDisease ⇣ ↳ KawasakiDisease	

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
Genomic Epidemiology Ontology[184]	entity ↳ continuant ⇣ ↳ specifically dependent continuant ⇣ ↳ realizable entity ⇣ ↳ disposition ⇣ ↳ disease ⋮ ↳ disease of anatomical entity ⋮ ⇣ ↳ cardiovascular system disease ⋮ ⇣ ↳ heart disease ⋮ ⇣ ↳ cardiac tuberculosis ⋮ ↳ cardiomyopathy ⋮ ↳ complete Kawasaki disease* ⋮ ↳ fulminant myocarditis ⋮ ↳ incomplete Kawasaki disease* ⋮ ⇣ ↳ disease or disorder ⇣ ↳ Mendelian disease ⋮ ↳ mucocutaneous lymph node syndrome ↳ cardiovascular disease ⋮ ↳ vascular disease ⋮ ⇣ ↳ vasculitis ⋮ ⇣ ↳ predominantly medium-vessel vasculitis ⋮ ⇣ ↳ mucocutaneous lymph node syndrome ↳ immune system disease ⋮ ↳ lymphoid system disease ⋮ ⇣ ↳ lymphatic system disease ⋮ ⇣ ↳ lymph node disease ⋮ ⇣ ↳ lymphadenitis ⋮ ⇣ ↳ mucocutaneous lymph node syndrome ↳ inflammatory disease ⇣ ↳ lymphadenitis ⋮ ↳ mucocutaneous lymph node syndrome ↳ vasculitis ⇣ ↳ predominantly medium-vessel vasculitis ⇣ ↳ mucocutaneous lymph node syndrome	Synonyms (for complete Kawasaki disease): - complete Kawasaki syndrome Synonyms (for incomplete Kawasaki disease): - incomplete Kawasaki syndrome Synonyms (for mucocutaneous lymph node syndrome): - MLNS - acute febrile mucocutaneous lymph node syndrome [MLNS] - acute febrile MLNS - Kawasaki's disease - infantile polyarteritis nodosa * These entries contain the following Editor's note: Planned Obsolescence: this term is a placeholder for a term requested in another ontology. Once the appropriate ontology term is available, this term's identifier will be obsoleted with a "term replaced by" id of the other term.

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
Human Dermatological Disease Ontology[185]	disease ↳ cutaneous disease ⇣ ↳ disorder caused by infections, infestations, stings, or bites ⇣ ↳ viral skin disease or viral disease with skin manifestations ⇣ ↳ kawasaki disease	Synonyms: - KD - mucocutaneous lymph node syndrome
Human Disease Ontology[186] and BioAssay Ontology[187] and Drug Target Ontology[188]	disease ↳ disease of anatomical entity ⇣ ↳ immune system disease ⇣ ↳ lymphatic system disease ⇣ ↳ lymph node disease ⇣ ↳ lymphadenitis ⇣ ↳ Kawasaki disease	Synonyms: - MLNS - acute febrile MLNS - mucocutaneous lymph node syndrome - acute febrile mucocutaneous lymph node syndrome - Kawasaki's disease
Human Health Exposure Analysis Resource[189]	Study Indicator ⇣ ↳ Health Outcome ⇣ ↳ Disease ⇣ ↳ lymphatic system disease ⇣ ↳ lymph node disease ⇣ ↳ lymphadenitis ⇣ ↳ Kawasaki disease	Synonyms: - MLNS - acute febrile MLNS - mucocutaneous lymph node syndrome - acute febrile mucocutaneous lymph node syndrome - Kawasaki's disease
Interlinking Ontology for Biological Concepts[190]	Life science research field ↳ Terms related to life science ⇣ ↳ Disease, and Symptom ⇣ ↳ Kawasaki disease ⇣ ↳ Acute phase Kawasaki disease ↳ gammaglobulin refractory Kawasaki disease ↳ incomplete Kawasaki disease	Synonyms: - Mucocutaneous lymph node syndrome
International Classification of Disease – 9th Edition[191]	VII. Diseases of the circulatory system (390-459) ↳ Diseases of arteries, arterioles, and capillaries (440-449) ⇣ ↳ 446: Polyarteritis nodosa and allied conditions ⇣ ↳ 446.1: Acute febrile mucocutaneous lymph node syndrome [MCLS]	

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
International Classification of Disease – 10th Edition[192]	XIII. Diseases of the musculoskeletal system and connective tissue (M00-M99) ↳ Systemic connective tissue disorders (M30-M36) ⇣ ↳ M30: Polyarteritis nodosa and related conditions ⇣ ↳ M30.3: Mucocutaneous lymph node syndrome [Kawasaki]	
International Classification of Disease – 11th Edition[193]	04. Diseases of the immune system ↳ Nonorgan specific systemic autoimmune disorders ⇣ ↳ 4A44 Vasculitis ⇣ ↳ 4A44.5 Mucocutaneous lymph node syndrome	
Medical Imaging and Diagnostic Ontology[194]	entity ↳ continuant ⇣ ↳ specifically dependent continuant ⇣ ↳ realizable entity ⇣ ↳ disposition ⇣ ↳ disease ⇣ ↳ disease of anatomical entity ⇣ ↳ immune system disease ⇣ ↳ lymphatic system disease ⇣ ↳ lymph node disease ⇣ ↳ lymphadenitis ⇣ ↳ Kawasaki disease	Synonyms: - MLNS - acute febrile MLNS - mucocutaneous lymph node syndrome - acute febrile mucocutaneous lymph node syndrome - Kawasaki's disease
Medical Subject Headings[195]	Cardiovascular Diseases ⇡ ↳ Vascular Diseases ⇡ ⇣ ↳ Vasculitis ⇡ ⇣ ↳ Mucocutaneous Lymph Node Syndrome ↳ Hemic and Lymphatic Diseases ⇡ ↳ Lymphatic Diseases ⇡ ⇣ ↳ Mucocutaneous Lymph Node Syndrome ↳ Skin and Connective Tissue Disorders ⇣ ↳ Skin Diseases ⇣ ↳ Skin Diseases, Vascular ⇣ ↳ Mucocutaneous Lymph Node Syndrome	Synonyms: - Kawasaki Syndrome

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
Mondo Disease Ontology[196]	disease or disorder ↳ cardiovascular disorder ⇣ ↳ vascular disorder ⇣ ↳ vasculitis ⇣ ↳ predominantly medium-vessel vasculitis ⇣ ↳ mucocutaneous lymph node syndrome ↳ primary central nervous system vasculitis ↳ thromboangiitis obliterans ↳ vasculitis due to ADA2 deficiency	Synonyms: - infantile polyarteritis nodosa - Kawasaki disease - acute febrile mucocutaneous lymph node syndrome [MCLS] - acute febrile mucocutaneous lymph node syndrome - Kawasaki's disease - acute febrile MCLS - Kd - Kawasaki syndrome - MLNS - mucocutaneous lymph node syndrome - infantile polyarteritis
National Cancer Institute Thesaurus[197] and Biological and Environmental Research Ontology[198]	Disease, Disorder, or Finding ↳ Disease or Disorder ⇣ ↳ Disorder by Site ⇣ ↳ Cardiovascular Disorder ⇣ ↳ Vascular Disorder ⇣ ↳ Vasculitis ⇣ ↳ Kawasaki Disease	Synonyms: - MLNS - acute febrile MLNS - mucocutaneous lymph node syndrome - acute febrile mucocutaneous lymph node syndrome - Kawasaki's disease
Neuroscience Information Framework (NIF) Standard Ontology[199]	continuant ↳ specifically dependent continuant ⇣ ↳ realizable entity ⇣ ↳ disposition ⇣ ↳ disease ⇣ ↳ lymphatic system disease ⇣ ↳ lymph node disease ⇣ ↳ lymphadenitis ⇣ ↳ Kawasaki disease	Synonyms: - acute febrile mucocutaneous lymph node syndrome - Kawasaki's disease - acute febrile MCLS - mucocutaneous lymph node syndrome - MLNS

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
Online Mendelian Inheritance in Man[200]	KAWASAKI DISEASE (i.e. exists as a top-level class)	Synonyms: - Infantile polyarteritis
Ontology of Consumer Health Vocabulary[201]	Concept ↳ UMLS_Concept ⇣ ↳ kawasaki disease	
Orphanet Rare Disease Ontology[202]	clinical entity ↳ disorder ⇣ ↳ Biological anomaly ↳ Clinical syndrome ↳ Disease ↳ Kawasaki disease ⇣ ↳ Malformation syndrome ⇣	Synonyms: - mucocutaneous lymph node syndrome
PLOS Thesaurus[203]	Medical and health science ↳ Immunology ⇣ ↳ Clinical immunology ⇣ ↳ Autoimmune disease ⇣ ↳ Kawasaki disease	
Radiology Lexicon[204]	RadLex ontology entity ↳ RadLex entity ⇣ ↳ clinical finding ⇣ ↳ pathophysiologic finding ⇣ ↳ infectious or inflammatory disease ⇣ ↳ inflammation ⇣ ↳ Kawasaki disease	Synonyms: - mucocutaneous lymph node syndrome

Continued...

Table 8.2 continued...

Ontology	Tree	Notes
Read Clinical Terminology Version 2[205]	Circulatory system diseases ↳ Arterial, arteriole and capillary disease ⇣ ↳ Polyarteritis nodosa and allied conditions ⇣ ↳ Acute febrile mucocutaneous lymph node syndrome ⇣ ↳ Acute febrile mucocutaneous lymph node syndrome NOS ↳ Kawasaki disease	
SNOMED CT[206]	Clinical finding ↳ Disease ⇣ ↳ Inflammatory disorder ⇣ ↳ Inflammation of specific body organs ⇣ ↳ Vasculitis ⇣ ↳ Systemic vasculitis ⇣ ↳ Primary systemic arteritis ⇣ ↳ Acute febrile mucocutaneous lymph node syndrome ↳ Polyarteritis nodosa ↳ Takayasu's disease	Synonyms: - Mucocutaneous lymph node syndrome
Systematized Nomenclature of Medicine, International Version[207]	DISEASES/DIAGNOSES ↳ Disease of cardiovascular system, NOS ⇣ ↳ Vascular disease, NOS ⇣ ↳ Disease of artery, NOS ⇣ ↳ Acute febrile mucocutaneous lymph node syndrome	Synonyms: - Kawasaki's disease
The Stroke Ontology[208]	Stroke ↳ Stroke type ⇣ ↳ Intracranial hemorrhage ⇣ ↳Etiology of hemorrhagic stroke ⇣ ↳ Vasculitis ⇣ ↳ Systemic vasculitis ⇣ ↳ Kawasaki syndrome	Synonyms: - Kawasaki disease

The National Center for Biomedical Ontologies (NCBO) was searched for all ontologies that referenced Kawasaki disease and related concepts. Many ontologies explicitly treat labels such as *Kawasaki disease* and *mucocutaneous lymph node syndrome* as synonyms. The ontological confusion around these condition labels is also clear: most ontologies categorise *Kawasaki disease / mucocutaneous lymph node syndrome* as a kind of disease (usually of the kind vasculitis or lymphadenitis) rather than a kind of syndrome. The Orphanet Rare Disease Ontology classifies *Kawasaki disease* (for which *mucocutaneous lymph node syndrome* is identified as a synonym) under the heading *Disease* and not under the heading *Clinical syndrome*. The Computer Retrieval of Information on Scientific Projects Thesaurus categorises *mucocutaneous lymph node syndrome* (for which *Kawasaki disease* is identified as a synonym) under both *disease* and *syndrome*. Finally, the Artificial Intelligence Rheumatology Consultant System Ontology categorises *Kawasaki disease* under *Examiner's diagnosis*.

While it is clear that labels like *Kawasakibyō*, *mucocutaneous lymph node syndrome*, *Kawasaki syndrome*, and *Kawasaki disease* are used interchangeably, I want to emphasise that they are not semantically isomorphic. In using a general term for illness, *Kawasakibyō* is essentially agnostic as to the ontological status of its referent. *MCLS* and *Kawasaki syndrome* are (potentially) more precise as to the ontological status of the referent: it is *the constellation of signs and symptoms* (i.e., the *syndrome*), which implies a unified underlying process. *Kawasaki disease* is ontologically ambiguous: if the technical meaning of *disease* is intended then the referent of *Kawasaki disease* ought to be *the unified underlying process*, of which the syndrome is a manifestation.[*] If the non-technical meaning of *disease* is intended then *Kawasaki disease* takes on the same ontological agnosticism as *Kawasakibyō*.

The language of these related concepts is clearly imprecise; however, the implications of that imprecision might readily be overlooked. In the section that follows I will seek to demonstrate what is lost by foregoing a more rigorous vocabulary.

Thought Experiments on the Ontological Status of "Kawasaki Disease"

Imagine that researchers uncover the case records and stored biological samples of a forgotten prospective cohort study of KD from before the introduction of intravenous immunoglobulin. Inclusion criteria were strict—all enrolled children fulfilled the diagnostic criteria for KD (i.e. had *complete Kawasaki disease*). Demographic and clinical details were recorded at diagnosis, and biological samples were stored. Cardiac outcomes (angiograms or echocardiograms) over the short and long term were also recorded. For the purpose of the thought experiment let us say that there were 1,000 children in the cohort, of whom 200[†] developed coronary artery aneurysms. The contemporary researchers undertake sophisticated analysis of the samples, with several possible findings—each with radically different implications for the ontological status of *Kawasaki disease*. For each of the scenarios described the following reflection is informative: *To what does the label Kawasaki disease refer?*

[*] The semantic confusion becomes even more apparent with terms like *Complete Kawasaki disease*. This typically connotes the fulfilment of the formal diagnostic criteria (as opposed to the modified criteria that might be fulfilled in a case of *incomplete Kawasaki disease*). This seems semantically closer to *Kawasaki syndrome*, albeit with greater implied precision.

[†] Following on from the earlier discussion on the published rates of coronary artery aneurysms prior to the use of IVIG, I have here assumed an aneurysm rate of 20%.

Scenario 1
Using highly sensitive metagenomic high-throughput sequencing[209] researchers identify a novel DNA virus in stored blood samples of all study participants. Subsequent analysis of samples from non-KD febrile controls is unable to identify the virus, which goes on to be named Human Kawasaki Virus (HKV).

> *Scenario 2*
> HKV is identified in all cases with aneurysms, but not in any other cases. A number of common childhood viruses (including adenovirus, enteroviruses, and human herpes viruses) are identified in the remaining cases.
>
> *Scenario 3*
> As for Scenario 1, however researchers identify two closely-related novel viruses—HKV-1 and HKV-2. HKV-2 is found only in cases with aneurysms.
>
> *Scenario 4*
> As for Scenario 1, however whole-genome sequencing identifies a single nucleotide polymorphism (SNP) in only those children who developed aneurysms. The affected gene is a critical regulator of the innate immune response.
>
> *Scenario 5*
> As for Scenario 2, however HKV is identified in 400 cases—including all who developed aneurysms.

Let us now consider how our concepts of KD might be influenced under these different scenarios. Scenario 1 most closely approximates the current Kawasaki Disease Paradigm. The clinical syndrome appears to map precisely to the entity *HKV infection*, and it appears that a subset go on to develop the entity *coronary artery aneurysm*.

In Scenario 2 we are forced to concede that the clinical syndrome that we now call *Kawasaki disease* (or, more precisely, *complete KD*) does not map on to any single disease process. At best the clinical syndrome functions as a non-specific clinical tool for finding cases of the entity *HKV infection*, which maps precisely to the entity *coronary artery aneurysm* (the actual entity of medical interest).

In Scenarios 3 and 4 all groups are ontologically coherent entities: the clinical syndrome maps onto the entity *HKV infection*, while the entity *coronary artery aneurysm* can be equated with a process—a particular *kind* of HKV infection (in Scenario 3), or a process of immune dysregulation triggered by HKV infection in genetically predisposed individuals.

Finally, Scenario 5 is like Scenario 2 except that the clinical syndrome lacks both specificity and sensitivity for the entities *HKV infection* and *coronary artery aneurysm*.

Paradigm Implications for Clinical Research

The importance of the ontological imprecision of the current KD vocabulary is exemplified in a recent study by Wright *et al*.[210] The authors describe a novel approach to developing a diagnostic test for KD by identifying a gene expression signature in circulating leukocytes. Samples were drawn from participants of a case-control cohort study of children with either KD[*] or another febrile illness (febrile controls). Blood was drawn prior to treatment with IVIG, and the transcriptome (the set of RNA transcripts isolated from peripheral leukocytes, indicative of the genes being actively transcribed) was characterised for each patient. A number of established machine learning algorithms were applied to identify a transcript signature that discriminated KD cases[†] from control cases. One novel algorithm (parallel regularized regression model search, written by the study team) identified a 13-transcript signature able to differentiate KD cases from febrile control cases with a sensitivity of 81.7% and a specificity of 92.1%.

This innovative approach to diagnostic research has the potential to revolutionise the clinical management of KD, however as currently conceived it remains firmly within the current paradigm. Put differently: the 2017 AHA diagnostic algorithm formed the *a priori* definition of KD, which the machine learning algorithm operationalised. This perpetuates the assumption that the ontological status of KD is best modelled by Scenario 1 described above.

An Alternative Paradigm

The purpose of diagnosis is to direct treatment to prevent adverse outcomes. An alternative paradigm ought to focus on the process by which adverse outcomes occur. History suggests such a paradigm:

> There exists an inflammatory disease process of which the development of coronary artery aneurysms is a consequence: infantile periarteritis nodosa (IPN)[‡]. Evidence of IPN exists in post-mortem reports dating back to the nineteenth century. In the decades after World War II, and in the context of an emerging epidemic, Japanese clinicians identified a set of clinical features by which IPN might be diagnosed in life (the *Classical Kawasaki*

[*] KD was defined according to the 2017 AHA diagnostic criteria.[1]
[†] Stratified by diagnostic certainty.
[‡] The label IPN is used here for historical continuity, however it is far from perfect. Recognition of "adult Kawasaki disease" presents one problem—not unlike that presented by Still's disease (adult-onset systemic juvenile idiopathic arthritis). The suggested (though almost certainly incorrect) relation to classical polyarteritis nodosa is also problematic.

> *Criteria*). Subsequent clinical trials proved that the inflammation of IPN in patients fulfilling the Classical Kawasaki Criteria could be ameliorated by treatment with IVIG.
>
> The cause of IPN remains unclear, however epidemiological evidence implicates an environmental or infectious cause. It is hypothesised that the Japanese population—largely isolated from the rest of the world since the start of the *Edo* period in 1603—was particularly naïve to this agent. Its introduction in the post-war period thereby preceded a dramatic epidemic of the disease, which continues to this day.
>
> In the absence of a diagnostic test for IPN the diagnosis remains clinical. In recognition of the suboptimal sensitivity of the Classical Kawasaki Criteria, researchers proposed the *Expanded Kawasaki Criteria*. The specificity of the Kawasaki Criteria has been difficult to determine. The large majority of children who fulfil the criteria have no evidence of IPN on echocardiogram; however, that diagnostic modality is imperfect[*], and IPN is known to cause lesions in other arterial beds. In light of this clinical uncertainty, IVIG is currently offered to all children who fulfil the Kawasaki Criteria.

This IPN-centred paradigm recognises the contributions of a generation of twentieth-century Japanese researchers (rather than Dr Kawasaki alone) for establishing clinical features by which cases of IPN might be diagnosed and treated life, rather than by pathologists after death. *Complete Kawasaki disease* is reframed as the *classical Kawasaki criteria*, and *incomplete Kawasaki disease* as the *expanded Kawasaki criteria*. The important distinction between the clinical syndrome and the disease entity is thereby made explicit: the *Kawasaki criteria* is a diagnostic tool for finding cases of IPN. Interrogating and refining the diagnostic performance (sensitivity and specificity) of that tool is therefore a valid and appropriate priority for clinical research.

The IPN Paradigm might better inform future research—particularly around aetiology and diagnosis. The methodology used in the study by Wright *et al* could be modified to discriminate IPN cases from non-IPN cases in a cohort of patients fulfilling the Kawasaki criteria. Discriminating IPN on the basis of echocardiograms early in the disease process can be challenging; many children in our prospective cohort study had mild coronary artery dilatation with subsequent normalisation[†]. Cases of delayed presentation thus present an opportunity in this regard. In our cohort, children with delayed diagnosis had coronary vessels that were either normal or markedly abnormal. A machine learning algorithm might have enhanced success identifying a

[*] Transthoracic echocardiography is insensitive to aneurysms of the posterior coronary arteries and distal coronary segments.[211]

[†] This may simply represent regression to the mean, especially allowing for an element of demand-driven physiological dilatation in the febrile phase.

transcriptome signature that discriminates those two groups—at least in the discovery phase.

Conclusions

The Kawasaki Disease Paradigm represents an important phase in the history of our quest to help children afflicted by this life-threatening condition, however its ambiguous language and lack of ontological precision limit its utility into the future. We must shift to a new paradigm that focusses on the pathological processes driving adverse coronary outcomes, rather than on clinical syndrome constructs.

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Appendix

In late 2019 reports began to emerge from China of a severe respiratory syndrome caused by a novel human coronavirus (named SARS-CoV-2). The disease—designated COVID-19—spread rapidly around the globe, causing significant mortality in some populations. Population-level data indicated very low morbidity and mortality in children, however case reports emerged of a very rare but devastating complication in that age group. Named *paediatric inflammatory multi- system syndrome temporally associated with SARS-CoV-2* (PIMS-TS) by the European Centre for Disease Prevention and Control, and *multisystem inflammatory syndrome in children* (MIS- C) by the US Centers for Disease Control and Prevention, the condition presented as a severe systemic inflammatory state, usually weeks after the acute SARS-CoV-2 infection.

The following manuscript, entitled "Update on the COVID-19-associated inflammatory syndrome in children and adolescents; paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2" was published in *The Journal of Paediatrics and Child Health* in 2020. It sought to summarise for Australian paediatricians the available literature with regard to PIMS-TS.

My contribution to this manuscript was Table 1. Representing a significant literature review, it compares and contrasts the case literature around PIMS-TS, Kawasaki disease, Kawasaki shock syndrome, and toxic shock syndrome. The insights that I gained from researching this piece informed my contribution to the work presented in Appendix Two.

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VIEWPOINT

Update on the COVID-19-associated inflammatory syndrome in children and adolescents; paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2

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We provide an update on the state of play with regards a newly described inflammatory condition which has arisen during the current SARS-CoV-2 pandemic. The condition has been named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 or multisystem inflammatory syndrome in children. This condition has shown significant similarities to Kawasaki disease and toxic shock syndrome.

Paediatricians and many families are aware of the recent reports of a novel multisystem inflammatory syndrome in children (MIS-C), which appears related to the ongoing SARS-CoV-2 pandemic. The condition has been named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by the European Centre for Disease Prevention and Control[1] and MIS-C by the Centres for Disease Control and Prevention in the USA[2] and World Health Organization.[3] Henceforth, we use the term PIMS-TS to denote both of these described entities.

PIMS-TS was first reported in the UK in late April through the European Union's *Early Warning and Response System* and has now been reported from other European centres, the USA and Middle East. Anecdotally, up to 1000 cases have been reported formally and informally. Fewer than 10 deaths have been publicly reported to date. No confirmed cases have been reported in Australia or New Zealand to date.

Overall, the reported infection rates with SARS-CoV-2 (the novel coronavirus) are lower in children than adults, and children are often asymptomatic or have comparatively milder acute manifestations.[4] Few children have required hospitalisation or intensive care admission as part of the acute infection.[5]

Rather than a manifestation of primary infection, PIMS-TS appears to be a severe but delayed immune response to SARS-CoV-2 infection with uncontrolled inflammation resulting in host tissue damage.[6] The finding that many children with PIMS-TS have positive SARS-CoV-2 serology but are PCR negative on nasopharyngeal swabs supports the hypothesis of a post-infectious phenomenon.[7–9] This is also supported by the observation that the peak in PIMS-TS cases lags behind the peak in acute SARS-COV-2 cases by some weeks.[7] The mechanisms are unknown, but it seems plausible that genetic variation in affected children may contribute to this rare syndrome. Both innate (non-specific) and adaptive (both humoral and T-cell mediated) arms of the immune system have been suggested to be involved.[9,10]

A striking feature of PIMS-TS is the overlap with Kawasaki disease (KD) and toxic shock syndrome (TSS), both vasculitides likely triggered by infection.[9] While SARS-COV-2 is the suspected aetiological agent causing PIMS-TS, the cause of KD is unknown and may involve more than one infectious trigger.[11] Interestingly another novel coronavirus (coronavirus New Haven – HCoV-NH/HCoV-NL63) was previously implicated as the possible cause of KD in a series of cases in 2005,[11] but this finding could not be substantiated in other populations.[12]

Children with PIMS-TS seem to present with a severe illness characterised by shock and features often seen in KD or Kawasaki shock syndrome (KSS) (a rare, more severe form of KD that shares features with TSS).[13] These features include prolonged fever, rash, conjunctival injection, mucosal changes and raised inflammatory markers. While these features are common to both KSS and TSS, the inflammation seen in PIMS-TS seems to be far greater than that of KD.[7–9,13] Other differentiating features of PIMS-TS include an older age of onset (average of 10 years compared to 2 years for KD) and abdominal pain and diarrhoea as prominent presenting symptoms; myocardial and renal dysfunction have also been reported.[7–9,13] Additionally, children with PIMS-TS have shown marked lymphopaenia and thrombocytopaenia, coagulopathy, raised cardiac enzymes (troponin and brain natriuretic peptide, BNP), hyponatraemia,

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Table 1 Kawasaki disease (KD), Kawasaki shock syndrome (KSS), toxic shock syndrome (TSS) and paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS): Comparison of key characteristics

Characteristic	KD	KSS	TSS	PIMS-TS
Biology				
Aetiology	Unknown. Infectious trigger in genetically susceptible host suspected.[18]	As for KD	*Staphylococcus aureus* producing TSST-1, SE-B, or SE-C. (A significant proportion of staphylococcal TSS cases are still menstrual associated.) *Streptococcus pyogenes* producing SPE-A or SPE-C[19]	Role of SARS-CoV-2 as trigger suspected, with a latent period of 1–4 weeks. Preceding SARS-CoV-2 infection may be asymptomatic
Pathophysiology	Systemic vasculitis with early activation of innate immune system (especially IL-1, IL-6, and TNF pathways)[18]	Unknown, but likely severe pathophysiology with shared features of both KD and TSS KD	SAG-mediated stimulation of T-cells causing massive cytokine release with capillary leak[19]	Unknown. Cardiogenic and distributive shock reported. Myocardial dysfunction may be related to acute systemic inflammation. Abnormal coagulation characteristic
Epidemiology (in paediatric population)				
Age, years – median	Peak age ~ 2 years[9,20]	Slightly older than KD[9,20]	Reported as a similar age (Whittaker *et al.*)[9] or older than KSS (mean 9.4 years in Lin *et al.*)[9,21]	Older than KSS (mean 9.6 years in Riphagen *et al.* and 9 years in Whittaker *et al.*)[7,9,22]
Sex ratio (male: female)	1.4:1[20]	Similar to KD[20,23]	1:9[24]	1.6:1[13] and 0.76:1[9]
Ethnicity	East Asian predominance[18,25]	No data	Caucasian predominance[24]	Afro-Caribbean prominence[9,13]
Incidence	Geographically widely variable. Australia: 17/100 000 *per annum* <5 years	5–7% of KD presentations[18,26]	~0.5/100000 *per annum*[19]	No data
Clinical presentation				
BP	N[18]	↓[27]	↓[28]	↓[7,13]
Oedema	Non-pitting, painful induration of hands and feet[18]	As for KD. May develop generalised oedema from capillary leak	Generalised non-pitting oedema from capillary leak	No data
Skin	Polymorphous rash, petechiae not typical. Late periungual desquamation	As for KD	Erythroderma, petechiae typical Late desquamation	Rash in around 50%[9,13]
Mucosa	Mucosal hyperaemia, ulceration not typical[18]	As for KD	Mucosal hyperaemia, ulceration typical[28]	Odynophagia in 3/8[13] and mucous membrane changes 29%[9]
Eyes	Non-purulent conjunctival injection	As for KD	Non-purulent conjunctival injection	Conjunctivitis in 45–62.5%[9,13]
Gastrointestinal	Abdominal symptoms (pain, diarrhoea, vomiting) common[18,20]	Abdominal symptoms (pain, diarrhoea, vomiting)more common than in KD[20]	Vomiting, diarrhoea, abdominal pain[28]	Diarrhoea in 50–87%[9,13] Abdominal pain in 50–75%[9,13]
Musculoskeletal	Arthralgia and arthritis common[18]	As for KD	Myalgia +++[28]	Myalgia in 1/8[13]
Neurological	Irritability common[18]	As for KD	Headache, confusion[28]	Headache in 25–25%[9,13]
Renal	Acute renal failure rare[20]	Acute renal failure more common than in KD[20]	Acute renal failure common[29]	22% with acute renal injury[9] and 1/8 required renal replacement therapy[13]
Echocardiogram findings				
Coronary changes	5–25%[22]	2–3 times more common than KD[20,27]	No data	14% have coronary lesions[9] Giant aneurysms in 12–25%[9,13]

(*Continues*)

Table 1 (Continued)

Characteristic	KD	KSS	TSS	PIMS-TS
Reduced EF	Rare[20]	Both cardiogenic and distributive shock reported frequently[20,23,30]	Reported, but distributive shock predominates[31,32]	Ventricular function abnormality in 31%[9] or 7/8.[13] Between 40 and 62% with shock had impaired EF[7,9]
Laboratory findings				
Total leukocyte count	N/↑[9,18,26]	↑[9,26]	N/↑[9,21]	N/↓[7,9]
Neutrophil count	N/↑[9,18,26]	↑[9,26]	N/↑[9,21]	N/↑[7,9]
Lymphocyte count	N[9,18]	N[9]	↑↑↑[9,28]	↓↓[7,9]
Haemoglobin	N/↓[9,26]	N/↓[9,26]	↓[9,21,28]	↓[7,9]
Platelet count	N, ↑↑ in 2nd–3rd week[18] ↓ in severe cases[18]	↑, however ↓ more common than in KD[9,21,27]	↓[9,21,28]	↓[7,9]
Fibrinogen	↑ initially, normalises rapidly[33,34]	N/↑[26,34]	↑[27]	↑[7,9]
D-Dimer	↑[34–37]	↑[9,34]	↑[9,28]	↑↑[7,9]
ESR	↑[21,26,34]	↑[21,26,34]	↑	↑[7,9]
CRP	↑[9,21,26,34]	↑↑[9,21,26,34]	↑↑[9]	↑↑[7,9]
Sodium	N	N/↓[38]	↓[28]	↓[7,9]
Creatinine	N[21]	↑[21]	↑[28]	
Albumin	N/↓ more in severe cases[9,18,20]	↓ more than in KD[9,20]	↓↓[9,28]	↓↓[7,9]
Bilirubin	N/↑[18]	No data	↑[39]	No data
Troponin	N[9]	N/↑[9,21,38]	No data	↑↑[7,9]
BNP	N	↑[37]	No data	↑↑[7]
Ferritin	N/↑[9,40,41]	↑[9]	No data	↑↑[7,9]
SARS-CoV-2 PCR	No data	No data	No data	Positive in 12–26%[7,9,13]
SARS-CoV-2 serology	No data	No data	No data	Positive in 80–87%[7,9]

BNP, brain natriuretic peptide; CRP, C-reactive protein; EF, ejection fraction; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction; SAG, superantigen; TNF, tissue necrosis factor.

hypoalbuminaemia and raised lactate dehydrogenase and ferritin; these features have only infrequently been reported in KD.[7–9]

Early reports suggest that 20–25% of PIMS-TS patients demonstrate coronary artery changes (similar to the rate in untreated KD[13]); however giant coronary artery aneurysms were uncommon (<4%),[9] and most lesions have resolved relatively promptly (over a few weeks) with treatment.[7,8,13]

As paediatricians are aware, KD has a much higher incidence in children of North East Asian ancestry[14,15]; it is notable that PIMS-TS has not yet been reported from Asia. Cases of PIMS-TS reported to date have shown a possible over-representation of children from African, African-American and Afro-Caribbean ancestry.[9,12] Hypothesised explanations for this observation include the effect of relative social disadvantage on disease exposure and transmission, as well as the possibility of a specific genetic predisposition to PIMS-TS (analogous but distinct from that contributing to the ethnic differences in KD incidence[15]).

Patients with PIMS-TS have often required supportive treatment for hypotension and circulatory collapse.[7–9,13] Intravenous immunoglobulin (also the primary treatment for KD) and corticosteroids have also been used extensively,[7–9,13] with biologic agents and anticoagulants used in selected cases on appropriate subspecialty advice. There have been a small number of deaths, but generally the outcomes have been good, with few patients requiring extracorporeal membrane oxygenation. The long-term cardiovascular outcomes are yet to be determined.

Interestingly, in early April clinicians in the USA reported a case of KD with concurrent COVID-19,[16] and paediatricians in France and Italy (both of which have had high incidence of SARS-CoV-2 infection) reported marked increases in KD diagnoses (without shock but with positive SARS-COV-2 testing).[7,8] Many of the cases reported had incomplete KD with fever and less than four of the cardinal 5 clinical features of KD.[7,8] However, other regions have not reported any increases in KD overall during the pandemic. In Australia and New Zealand, where community transmission and incidence of SARS-CoV-2 remains low, there has not been any change in expected KD incidence in 2020 to date in as yet unpublished national surveillance data (http://www.paeds.org.au/covid-19-kawasaki-disease-kd-and-pims-ts-children).[17]

At present, little is known about PIMS-TS. It is unclear whether PIMS-TS represents a severe form of KD triggered by SARS-CoV-2, or a separate entity with a spectrum of disease extending from a mild febrile illness through a KD-like illness to a severe KSS/TSS-like disease. As KD, KSS and TSS are all syndromic, with no diagnostic test, as shown by Whittaker *et al.*,[9] it is difficult to define the boundaries between these phenotypes (Table 1).

We suggest that clinicians should be aware of this new condition and in the current pandemic should consider PIMS-TS when assessing children with fever and a differential diagnosis of KD, TSS, fever and rash, severe abdominal pain or shock without obvious cause. As with any serious paediatric condition, clinicians should follow recommended clinical management pathways for COVID-19, KD or TSS. For any patient with these conditions suspected to have PIMS-TS, it is important to ensure testing for SARS-CoV-2 by PCR on appropriate specimens but to also collect a blood sample for testing of antibodies (serology) to SARS-CoV-2 prior to IVIG therapy along with convalescent serology. Suspected cases should be discussed with local specialist paediatric services (infectious diseases, rheumatology, intensive care, cardiology) as appropriate.

In Australia and New Zealand, few if any cases of PIMS-TS would be expected if community transmission of SARS-CoV-2 is low – particularly in children. Nevertheless, the Paediatric Active Enhanced Disease Surveillance network, which already conducts national surveillance for KD and other conditions relevant to paediatrics (www.paeds.org.au) and The Influenza Complications Alert Network are working to establish active surveillance for PIMS-TS in Australia. These groups will be collaborating with other networks to ensure cases of PIMS-TS are rapidly detected and comprehensively investigated. For further information about surveillance and standardised data collection, please refer to http://www.paeds.org.au/covid-19-kawasaki-disease-kd-and-pims-ts-children

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