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Kawasaki Disease - A prospective population survey in the UK and Ireland from 2013-2015.

Robert M R Tulloh (1,2), Richard Mayon-White (3), Anthony Harnden (3), Athimalaipet V Ramanan (1,2), E. Jane Tizard (1), Delane Shingadia (4), Colin A Michie (5), Richard M Lynn (6), Michael Levin (7), Orla D Franklin (8), Pippa Craggs (2), Sue Davidson (9), Rebecca Stirzaker (10), Mike Danson (10), Paul A Brogan (4).

Bristol Royal Hospital for Children, Bristol, UK (1); Bristol Medical School, University of Bristol, Bristol UK (2); University of Oxford, Oxford, UK (3); UCL Great Ormond Street Institute of Child Health, London, UK (4); Ealing General Hospital, London, UK (5); British Paediatric Surveillance Unit, Royal College of Paediatrics, London, UK (6); Imperial College, London, UK (7); Our Lady's Children's Hospital, Dublin, Ireland (8); Kawasaki Disease Support Group, Coventry, UK (9); Heriot-Watt University, Edinburgh, UK (10)

Corresponding author

Professor Robert M R Tulloh,

Department of Paediatric Cardiology,

King David Building, Upper Maudlin Street

Bristol BS2 8BJ

Email Robert.Tulloh@bristol.ac.uk

Tel +441173428856 Fax +441173428857

Running Title

Kawasaki Disease in UK and Ireland

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Abstract

Objectives

Kawasaki disease (KD) is an increasingly common vasculitis with risk of coronary artery aneurysms (CAA). The last UK survey was in 1990 whereas current epidemiology, treatment patterns, and complication rates are unknown, and the aim of this study was to address that knowledge gap.

Methods

A British Paediatric Surveillance Unit (BPSU) survey in the UK and Ireland from 01.01.2013 to 28.02.2015 ascertained demographics, ethnicity, seasonal incidence, treatment, and complication rates.

Results

553 cases were notified: 389 had complete KD; 46 had atypical KD; and 116 had incomplete KD, two diagnosed at post-mortem with incidence 4.55/100,000 children under 5 years, male: female ratio 1.5:1, median age 2.7 years (2.5 months-15 years). Presentation was highest in January and in rural areas. Most were White (64%); Chinese and Japanese Asians were over-represented as were Black African or African mixed-race children. 94% received intravenous immunoglobulin (IVIG). The overall CAA rate was 19%, and all-cardiac complications affected 28%. Those with CAA received IVIG later than in those without (median 10 days vs 7 days). Those under 1 year had fewer symptoms, but highest CAA rate (39%). Overall 8/512 cases (1.6%) had giant CAA; and 4/86 cases (5%) under 1 year of age developed giant CAA. Mortality from KD was 0.36%.

Conclusions

The UK and Ireland incidence of KD has increased and is more frequently seen in winter and rural areas. Delayed IVIG treatment is associated with CAA suggesting earlier and adjunctive primary treatment might reduce complications to prevent CAA, particularly in the very young.

BACKGROUND

Kawasaki Disease (KD) is a self-limiting medium vessel vasculitis of unknown aetiology that typically presents in children and adolescents with fever and muco-cutaneous changes. If left untreated, 15-25% of children will develop coronary artery aneurysms (CAA); 2%–3% of untreated cases die as a result of coronary vasculitis causing myocardial ischaemia, sometimes many years later [1]. The incidence of KD varies from 264 per 100,000 children under 5 years in Japan, to about 5-8 per 100,000 in England [2 3]. The high rate in North East Asians, which persists after migration to countries with low incidence [4], is strong evidence for a genetic factor and there is clear evidence from genome wide association studies of an important role for genetic variants in determining susceptibility. The aetiology of KD is unknown, but seasonal variation, occurrence of epidemics and association with wind patterns would be compatible with an infectious or toxic trigger [5 6].

KD is the commonest cause of acquired heart disease in children in the UK and USA [7 8]. Prompt diagnosis is essential to minimize complications. Intravenous immunoglobulin (IVIG) has formed the mainstay of primary treatment following publication of a seminal clinical trial in the 1980s [9]. However, IVIG-resistance occurs in up to 20-40% of unselected cases and is associated with increased coronary complication rates [1 10]. Recent studies and meta analyses of all published studies have suggested that addition of corticosteroids to IVIG reduces the risk of CAA, particularly in high risk patients [1 10 11]. However, there is currently no reliable method to predict which patients are at risk of CAA and thus require additional treatment, as scoring systems that predict IVIG non-response in Japan have not been reliable in studies in UK and North America.

The last comprehensive epidemiological study of KD in the UK was undertaken by the British Paediatric Surveillance unit (BPSU) in 1990 [12]. This revealed an incidence of 3.4/100,000 children under 5 years from January 1st to 31st December 1990; and a higher than expected coronary complication rate of 29% in those

children who had received IVIG, comparable to those patients who did not receive IVIG. More recent epidemiological studies noted a higher UK incidence of 8.39-9.1/100 000 children under the age of 5 [3 8], but both were limited by indirect retrospective epidemiological methodologies, and thus may not be accurate. Moreover, 24% of children with KD are older than five years [13 14 15], but accurate UK epidemiological data are lacking in this age group.

The incidence of KD has been reported to be increasing in many countries. Furthermore, the population demographics are changing, and there is therefore a need for updated information on KD in the UK [1 16 17]. The purpose of this study was to establish the current incidence of KD in the UK, noting the seasonal variation; to assess complication rates and the factors influencing these; and to shape future management practice based on these data (Panel 1). Areas of particular interest included the potential influence of ethnicity, urbanisation, and disease outcomes in the light of recently updated clinical guidance regarding the use of corticosteroids for KD [1].

Panel 1: Summary of Kawasaki disease BPSU research questions

Incidence:

- What are the demographics (sex, age, ethnicity, area of residence) of those diagnosed with Kawasaki disease (KD) in the UK and Ireland less than 16 years old?
- Has the incidence changed since the last survey in 1990?

Clinical Presentation and cardiac complications:

- How does KD first present, and what is the interval between first presentation and diagnosis?
- What is the frequency and nature of cardiac complications detected using echocardiography within 30 days of developing KD?

Clinical Management:

- What acute treatment is being given to patients during their initial hospital presentation with KD?
- Are treatments other than aspirin and intravenous immunoglobulin being used, and if so, has this impacted on outcome?

Other Outcomes:

- What is the frequency of non-cardiac complications within 30 days following KD?
- How are patients with KD being followed up within the UK and Ireland?

METHODOLOGY

The study used BPSU methodology for the epidemiological research surveillance, similar to the 1990 BPSU KD survey [12]. Each month all paediatricians and paediatric cardiologists (list available from the Royal College of Paediatrics and Child Health and the British Congenital Cardiac Association) were contacted by email to report if they had seen a case of KD. If notified, the BPSU would then make the research team aware and a questionnaire was posted. This surveillance methodology provided an active, real-time quantitative portrait of KD in the defined population. All of the UK and Ireland were included in the study. Also included were the Channel Islands and Isle of Man. Incidence was calculated by applying the most recent resident population data from the 2011-2015 Census of Population [18] and their equivalents from Ireland [19]

Panel 2 KD Case definition

Any infant or child up to the age of 16 years presenting for the first time in the UK or Ireland with fever of 5 or more days duration *plus* 4 of the following (complete KD), or *plus* any 3 of the following (incomplete KD) or *plus* 2 or 3 of the following with coronary artery changes (atypical KD):	
1. Conjunctivitis	Bilateral, bulbar, non-suppurative
2. Lymphadenopathy	Cervical > 1.5cm
3. Rash	Widespread, polymorphous. *Not* vesicular.
4. Lips and mucosa	Red cracked lips, 'strawberry tongue', erythematous oral cavity
5. Changes of extremities	Erythema, oedema of palms and soles initially, later peeling of skin

Inclusion criteria

In the first year, the protocol requested the reporting of only Complete KD cases, but in the second year all cases of KD (i.e. including atypical and incomplete KD as per the aforementioned definitions) were included. Where the interpretation of clinical features was uncertain, expert panel review (RT, RMW, AR, JT, DS, PB) of the case was undertaken to ascertain by consensus (defined as 100% agreement among experts) if the diagnostic criteria for KD had been fulfilled, and if so how to classify the subtype of KD (complete, atypical, or incomplete) for inclusion in the study.

Exclusion criteria

Exclusion criteria were patients older than 16 years; outside the pre-defined study period; and those with alternative final diagnoses. In addition, for the first year of the study, those with streptococcal infection were excluded, but not in the second year of study, since it is now recognized that streptococcal infection (and other infections) may be associated triggers for responses resulting in KD [20].

Cardiac involvement

We defined coronary artery aneurysms (CAA) as Z score of $\geq$ 2.5 internal diameter [21]. The Z scores were checked or completed, using Cardio Z software, based on the data supplied by Dallaire and Dahdah [22]. Those with aneurysms were referred to as CAA+ and those without were CAA-. In addition, there were some children with bright coronary artery walls, dilated (but non-aneurysmal) coronary arteries, pericardial effusion, or myocarditis. These were recorded as cardiac involvement, but not CAA. We recorded the early presence of CAA at diagnosis, and also in some cases later echocardiographic data was also presented. Giant aneurysms were defined as ≥8mm or z score ≥10 [23].

DURATION OF THE STUDY

In accordance with the most recent BPSU methodology, data collection was over a 25-month period, Jan 2013 – Feb 2015. All data was collected and retained in accordance with the Data Protection Act 1998.

DATA MANAGEMENT, ANALYSIS AND SECURITY

As approved by the ethics committee, parental consent was not obtained as the identity of the cases was known only to the reporting clinician. Anonymous questionnaires were sent from our study centre after case notification. Use of the NHS number and date of birth allowed checks for duplication. Using the first four components of the postcode, the population density was estimated by area where each patient lived in the UK and by area in Ireland. As most of the data were categorical or not normally distributed, statistical methods based on the Chi-squared test were used., Statistical analysis was undertaken at Heriot-Watt University (MD, RS) using SPSS, version 24. A *p* value of <0.05 was considered significant. The distribution of numerical values was summarized as medians and ranges; the Wilcoxon-Mann-Whitney test was used for group comparisons of those with or without CAA. A complex System Level Security Protocol (SLSP) was utilized and was risk assessed on an annual basis.

ETHICAL APPROVAL

National Research Ethics Committee 11/SW/0310

NHS Sponsorship CS/2011/3847

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RESULTS

Between 1 January 2013 and 28 February 2015, 601 reports of KD were received by the BPSU, with 38 duplicates, 9 other diagnoses and one with no clinical information. Of the remaining 553, there were 389 cases of complete KD; 46 atypical cases with fewer than four clinical features but with abnormal echocardiograms; and 116 cases of incomplete KD. Two cases were diagnosed retrospectively at post-mortem without any clinical data to allow KD-subtype categorisation (Table 1).

Males comprised a significantly greater proportion of the cases, and the proportion of Black and Asian patients was increased relative to the expected proportion of these groups in the population (Table 1) [18]. There were significantly more children under 1 year old with atypical or incomplete KD (45/95; 47%), compared with children over 1 year old (102/428; 24%) (Chi-squared = 21.31 $p<0.0001$).

The annual incidence was estimated using the 257 cases that had been diagnosed between 1 February 2014 and 31 January 2015, and whose ages were reported since only in the second year were all sub-types of KD reported.

The age-specific annual incidences were 4.55/100,000 at age 0-4 years; 1.26/100,000 at 5-9 years, and 0.08/100,000 at 10-14 years.

Date of diagnosis

Based on 479 cases reported between1st February 2013 and 31st January 2015, more cases occurred in the winter (defined as December – February) and spring (March - May) than in the summer (June - August) and autumn (September – November) months (Figure 1) (Chi-squared tests for monthly and seasonal variations were significant at p=0.08). These results controlled for length of month and confirmed the appreciable peaks in January in both 'all' and 'complete' cases.

Time to first point of clinical contact and diagnosis

443 (80%) children saw a general practitioner (GP) at median (range) 2 (0-27) days from the first onset of symptoms. The time from first GP consultation to hospital admission was 1 (0-32) days; time from disease onset to formal diagnosis was 7 (0-36) days; and time to diagnosis following admission to hospital was 1 (0-25) days, with 50 cases being diagnosed on day of admission.

We used the first four components of the postcode of patients in the UK to assign cases as resident in Urban or rural areas and compared the proportion of cases occurring in rural or urban areas. Relative to the population density we found significantly more cases occurring in rural areas (applying a non-linear cubic regression offered best fit with $R^2 = 0.867$, $F=30.290$, $p<0.005$) (Figure 2).

CLINICAL FEATURES

Coronary artery status

The results of the initial echocardiograms were available for 523/553 children. There were 11 children in whom the weights and Z scores were missing, so these have been omitted from analysis. Overall, 123/512 (24%) had abnormal coronary Z score (Z score >2) at echocardiography within 30 days of diagnosis. Of these, 95/512 had coronary Z score ≥ 2.5, thus the overall CAA rate within 30 days of diagnosis was 19%.

In 25 children, there was a pericardial effusion recorded, and in 7 there was either valve regurgitation or depressed ventricular function. Taking these into account, the all-cardiac complication rate (coronary Z>2, or any other cardiac complication) was 28% within 30 days of diagnosis (Table 2). It is of note that a much higher proportion of children under the age of 1 year had CAA+ (39%) compared with those over the age of 1 (13%, $p<0.01$). Overall, 8/512 cases (1.6%) developed giant CAA, and 4/86 cases (5%) under 1 year of age had giant CAA.

Variables associated with coronary artery aneurysms

We reviewed the association of CAA status with features highlighted in previous publications (Table 3) to determine whether there were any associations with CAA [24] [25]. In addition, we explored if there were any differences in coronary outcomes between 2013 and 2014, which may have been influenced by the publication of a new UK clinical guideline paper at the end of 2013 [1]. In 28 cases, we did not know the coronary artery status; and in both of the post mortem cases there were coronary artery aneurysms.

The presence of fever plus four diagnostic features of KD at the time of diagnosis (complete KD) was associated with a lower rate of coronary artery involvement. Younger age at presentation; longer time to receive treatment; and presentation between December and May were all associated with increased risk of CAA. Additional factors associated with the presence of CAA were lower albumin, and higher corticosteroid use in those with CAA (Table 3).

Treatment with IVIG and aspirin

Excluding the 2 cases diagnosed after death, and excluding the 20 cases with incomplete data, 502/531 received IVIG (95%), with the recommended dose of 2g/kg (97%). 29/531 (5%) did not receive IVIG: 20 with complete KD; 0 with incomplete KD; and 8 with atypical KD, (one not classified). The usual reason for not giving IVIG was delayed diagnosis, but in one case the parents refused therapy (Table 3). Anti-inflammatory dose aspirin (30-50 mg/kg/day, divided into four daily doses) was given to 472/537; 41 did not receive any aspirin; data regarding aspirin were missing for the other cases. Following this, an anti-platelet dose of aspirin (3-5mg/kg once a day) was given to 460 (83%) children. As shown in Table 4, the proportion of patients with CAA was lowest in those treated with IVIG within 7 days of onset and increased progressively in the group treated between 7 and 10 days and above 10 days.

Adjunctive therapy

Overall, corticosteroids were used in 49/512 (10%) cases where CAA status was documented, either as primary adjunctive (4.6%), or as late rescue therapy (4.8%) (Table 3). Infliximab was given to 10/551 cases (1.8%). Many children were commenced on antimicrobials (n=73) before the diagnosis of KD was made. No other treatments were reported.

Other outcomes

Of the 523 cases with echocardiography performed within 30 days of diagnosis, data on follow up echocardiography beyond 30 days were available in 49/523 of which 40/49 had persistent CAA. Overall, 8/49 had persistent giant CAA, including the 4 cases of giant CAA under the age of 1 year. Three had arthralgia, one had anaemia, one had hypertension, and one had lethargy. In addition to the 2 cases who were diagnosed after death,

a third child with pre-existing neurological disease died from intractable seizures, providing an all-cause mortality rate of 3/553 (0.54%), and mortality directly attributable to KD of 2/553 (0.36%).

DISCUSSION

This prospective UK population-based study shows that the incidence of KD as reported by paediatricians in the UK and Ireland has risen since the last survey in 1990 (from 3.4 to 4.55/100,000 children under 5 years, with male: female ratio of 1.51:1. It is noteworthy that estimates of KD incidence based on hospital admission or GP database statistics previously reported more than double the number of cases in our survey [8] [26]. This BPSU survey used rigorous diagnostic criteria to ensure accurate case inclusion. In contrast hospital admission data are not based on strict epidemiological KD case definitions, usually relying on diagnoses assigned by junior doctors or coding clerks and are thus likely to significantly over-record KD cases. Conversely, the voluntary reporting system used by the BPSU could under-record cases, as busy paediatricians may not respond or recall all the cases or may believe their colleagues are doing the reporting. Therefore, our BPSU data are likely to provide a minimum estimate of annual incidence. Many features observed in this UK and Ireland study are also seen in studies from other countries, including the majority of cases being less than 5 years old, seasonal occurrence with more cases in winter and spring, and increased proportion of Chinese or Japanese Asians and Black Africans relative to their proportion in the general population. We found an increased proportion of cases lived in rural areas relative to the population distribution. Early (within 30 days) all-cardiac complication rates for this unselected treated UK population were 28%; 19% had CAA at 6 weeks, based on a coronary Z score ≥2.5 (Table 2). Worryingly, 39% of KD patients under 1 year of age developed CAA despite IVIG; and mortality rates at 0.36% were approximately 10-fold lower than the last BPSU study.

We were surprised that residence in urban areas was associated with lower incidence of KD than rural residence. There might be many different explanations for this finding, including greater exposure to toxins used in farming, agriculture associated microorganisms, or increased exposure to pollens [3]. The suggestion that wind patterns could propagate triggers might be of relevance in this context [6].

There was a change in the case ascertainment protocol from the first year of the study to the second. We were obliged by the BPSU reporting restrictions to have a small number of cases (less than 300 in each year) and there was concern that including all cases of KD would make the total number too large. However, it was clear, during the first year of study, that we were being notified of incomplete cases and that we were not going to exceed 300 cases per year. In addition, there was a new guideline that was published during the time of the study advising steroids in high risk cases. We wished to capture both of these pieces of information. Clearly, the incidence of all cases of KD could therefore only be based on the second year of study. Despite this, we saw little difference in the demographics between the two years.

We found that the frequency of CAA (19%), is lower than the 29% observed in the treated cases in the original 1990 BPSU study[27], but significantly higher than CAA rates previously reported from other countries[23] and comparable to reported coronary sequelae rates for untreated cases [1 17]. This adds weight to our belief that the rise in observed incidence is not due to better case ascertainment, but due to a real increase in number of cases and also case severity. Similarly high CAA rates have now also been observed in Sweden [28] and Russia [29] with delayed diagnosis cited as a likely explanation for high coronary complication rates in the latter study. We found that the proportion with CAA was lowest in patients treated within 7 days, and this increased with later treatment. Our data therefore strongly suggest that delayed diagnosis and treatment is a significant factor contributing to the high incidence of CAA in the UK. Furthermore, the low numbers of patients receiving adjunctive treatments such as corticosteroids or anti-TNF, which are associated with more rapid resolution of inflammation and reduced CAA

risk, suggests many UK KD patients are not receiving optimal therapy advised in national and international guidance [1].

Our study confirms that children under 1 year are more likely to have atypical KD and higher rates of coronary sequelae (39%), as reported in other series [1]. Diagnosis of KD is difficult in the absence of all the typical features. As a high proportion of infants under 1 year of age do not fulfil the KD diagnostic criteria, there is a need for increased awareness of the possibility of KD in any infant with evidence of persistent inflammation (raised CRP, ESR or white cell count) and no response to antibiotics. In these infants, echocardiography is an urgent investigation required as part of the diagnostic work up of suspected incomplete KD. A high index of suspicion is thus required, and early treatment with IVIG and additional anti-inflammatory agents, and referral to specialist units for suspected atypical KD cases in view of the high risk of CAA is advised. Our findings also support the previous suggestion that children under 1-year should be regarded as high risk for coronary sequelae [1], and therefore be targeted for more aggressive primary treatment. It is also of note that there was a higher rate of CAA in children in the second half of the study, after 1.2.2014. The most likely reason for this is that we included atypical KD in the second half of the study, which have CAA by definition.

Ninety-four % of children received IVIG in line with current guidance along with high dose aspirin in almost all, although as previously highlighted, those children with CAA+ were treated later (median 10 days) than those without CAA (7 days), highlighting the importance of instituting treatment as early as possible (i.e. not just within 10 days) to improve outcomes [30].

Corticosteroids were only used in 10% of cases (Table 3); 4.6% of cases as primary therapy, and as rescue therapy in 4.8%. This overall relatively low use of corticosteroids, combined with delay in initiating treatment, could

explain the high CAA rates we observed since a recent meta-analysis of 2746 patients has now demonstrated that early addition of corticosteroids is associated with reduced risk of CAA compared with IVIG therapy alone, particularly for high risk cases (odds ratio 0.424; 95%CI, 0.270-0.665) [30]. Arguably, however, all UK KD patients could be deemed "high-risk", since 19% developed CAA within 30 days despite IVIG treatment, with even higher risk for children under the age of 1 year, of whom 39% developed CAA, of which 5% had giant CAA with poor prognostic outcomes. We would have liked to have had follow-up on the CAA after 30 days, but we were obliged by our protocol approval by the BPSU and National Information Governance, to keep this within the acute phase. We hope to be able to return to these patients and obtain ethical approval and consent for a follow-up study in the future.

Limitations.

BPSU methodology relies on busy doctors to complete data entry, and thus a surveillance-based study of this nature is limited since it is entirely dependent on the entry of data and case ascertainment for completeness. Therefore, although ours was a prospective study, it is expected that there will be a small proportion of cases that are not reported as evidenced in a recent German study suggesting that up to 44% of cases can be missed [31]. This will only serve to increase the incidence of KD above that in the present reported study. Also, by the nature of BPSU study methodology, follow up data examining late cardiac sequelae are limited.

CONCLUSIONS

KD has a rising incidence in the UK and Ireland, and cardiac sequelae are higher than reported for other countries despite most patients receiving IVIG therapy. Treatment delay is likely to have been contributory to high CAA rates. A future National UK comparative clinical trial of corticosteroids as primary adjunctive therapy for unselected KD patients is now planned. In the meantime, general practitioners and paediatricians should be aware that

treatment to completely ablate systemic inflammation as early as possible is required to prevent lifelong cardiac sequelae, and that the historic KD therapeutic adage of “treatment within 10 days” is no longer fit for purpose.

WHAT IS ALREADY KNOWN ON THIS TOPIC

1. Kawasaki Disease is the commonest acquired heart disease in the western world, with highest incidence in North East Asians and with unknown aetiology.

2. Seasonal variation, with peaks in winter and spring, and reported epidemics suggest that there are environmental factors, which trigger the condition.

3. The original BPSU study in 1990 suggested that UK patients might have high CAA rates despite IVIG.

WHAT THIS STUDY ADDS

1. There is a rising incidence of KD compared to 1990, with increased incidence in Chinese and Japanese Asians, and in children of Black African descent; and increased incidence in rural populations.

2. Children under 1 year are at highest risk of CAA (39%) and are more likely to present with atypical KD.

3. The overall frequency of CAA remains high at 19% despite more widespread use of IVIG, although mortality is now 10-fold lower than documented in 1990. Late diagnosis and treatment is associated with coronary artery aneurysms.

Authorship contribution

RT, AH, RMW, PB and RL designed the project. Cases were assessed by the expert panel review (RT, RMW, AR, JT, DS, PB) and PC collected and recorded the data. SD provided patient participation support and informed families involved in the study of ongoing progress. CM, AH and OF provided local support and

assisted with recruitment. RMW, RS and MD undertook statistical analysis. All authors satisfied the contributorship requirements.

Figure legends

Figure 1. Incidence of KD by month at diagnosis, showing breakdown into complete, atypical and incomplete cases. PM was diagnosis at post-mortem.

Figure 2. Plot of urbanicity (as assessed by population per postcode, per sq km) against number of cases of KD.

Table 1. The demographics of Kawasaki disease in the UK and Ireland.

		Complete		Atypical		Incomplete		Post-mortem		Total	
Total No of cases		389	%	46	%	116	%	2	%	553	100%
Sex	Male	231	60%	28	61%	64	55%	0		323	59%
	Female	153	40%	18	39%	42	36%	2	100%	215	39%
	Sex unreported	5	1%	0	0%	10	9%	0		15	3%
	Male:Female ratio	1.50:1		1.56:1		1.52:1		0		1.51:1	
Age (years)	<1	50	13%	20	43%	25	22%	2	100%	97	18%
	1-4	251	64%	19	41%	48	41%	0		318	57%
	5-9	69	18%	5	11%	28	24%	0		102	18%
	10-16	7	2%	1	2%	1	1%	0		9	2%
	Not reported	12	3%	1	2%	14	12%	0		27	5%
Ethnicity	White	257	75%	26	70%	71	72%	1	50%	355	64%
	White & Black	12	6%	4	5%	4	2%	0		20	7%
	White & Asian	10	2%	1	2%	3	0%	0		14	2%
	Black	39	3%	4	6%	3	0%	0		46	4%
	Asian sub-continent	25	7%	5	8%	12	9%	0		42	10%
	Other Asian	11	5%	1	8%	3	7%	1	50%	16	8%
	Chinese/Japanese	14	3%	4	2%	2	9%	0		20	5%
	Others	21	5%	1	2%	18	16%	0		40	7%
Country	Scotland	19	5%	3	7%	7	6%	0		28	5%
	Republic of Ireland	23	6%	0	0%	9	8%	0		31	6%
	Wales	24	6%	7	15%	6	5%	0		35	6%
	N. Ireland	9	2%	0	0%	2	2%	0		12	2%
	IoM/Channel Islands	2	1%	2	4%	1	1%	0		5	1%
	England	312	80%	34	74%	94	79%	2	100%	442	80%
Date of illness	1.2.13-31.1.14	186	49%	13	28%	27	25%	0		226	42%
	1.2.14-31.1.15	161	42%	30	65%	70	60%	2	100%	263	49%
	Outside study period	36	9%	3	7%	9	8%	0		48	9%

Table 2. Echocardiographic data showing Cardiac complications. There were 11 children in whom the weights and z scores were missing, which have not been included in the table.

Time of Echo	Number assessed	Coronary z<2	Coronary 2≤z<2.5	Coronary 2.5≤z<5	Coronary 5≤z<10	Coronary z≥10	Pericardial Effusion	Valve regurgitation
At Diagnosis	523	389	28	59	28	8	25	7
>30 days	49		9	20	12	8	0	0

Table 3: Association of coronary artery status with individual variables. CAA+ = those with coronary artery aneurysms. CAA- = those without aneurysms. IVIG = intravenous immunoglobulin. *P* value is difference in median: ns = not significant. The numbers of patients receiving corticosteroids were too small for meaningful statistical testing. There were 11 children in whom the weights and z scores were missing, which have not been included in the table.

Criterion	CAA+ (*n*=95)	CAA- (*n*=417)	*P* value
Male	62 (69%)	247 (59%)	0.27 ns
Median lowest Albumin g/L **Range**	26 (13, 41) *n*=83	31 (21, 49) *n*=372	0.049
Median Lowest Sodium mmol/L **Range**	134 (125, 142) *n*=48	134 (123, 141) *n*=210	0.92 ns
Median Lowest Platelet count x10^9/L **Range**	212 (30, 442) *n*=95	245 (54, 450) *n*=415	0.15 ns
Median Age months at presentation **Range**	21.6 (2.4, 190.0) *n*=93	36.0 (1.2, 190.0) *n*=409	0.005
Median Time to treatment (days) **Range**	10.0 (2, 37)	7.0 (1, 36)	0.005
Mucosal involvement at diagnosis	77/95 (81%)	360/416 (87%)	0.19 ns
Dec-May presentation	64/95 (67%)	245/416 (59%)	0.12 ns
Presentation before 1.2.2014	53/95 (56%)	210/416 (50%)	0.35 ns
Primary steroid use	11/95 (12%)	13 (3%)	
Late corticosteroid use	13 (14%)	12 (3%)	
No corticosteroid use	67/92 (73%)	359/384 (93%)	0.03

Table 4: Association of time of treatment with Intravenous immunoglobulin (IVIG) with coronary artery aneurysms. Numbers were small, so statistical comparison of these groups was not performed. Absolute numbers with % in brackets

	Age <1 year				Age >1 year			
IVIG timing	Number of cases	Z<2.5	Z≥2.5	missing	cases	Z<2.5	Z≥2.5	missing
IVIG before day 7	45	33	11	1	160	138	17	5
IVIG day 7-10	28	12	15	1	142	116	23	3
IVIG>day 10	14	3	9	2	79	62	15	2
No IVIG or missing	8	4	2		49	41	1	

References

1. Eleftheriou D, Levin M, Shingadia D, et al. Management of Kawasaki disease. *Archives of disease in childhood* 2014;99(1):74-83. doi: 10.1136/archdischild-2012-302841
2. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2009-2010 nationwide survey. *Journal of epidemiology / Japan Epidemiological Association* 2012;22(3):216-21.
3. Harnden A, Mayon-White R, Perera R, et al. Kawasaki disease in England: ethnicity, deprivation, and respiratory pathogens. *The Pediatric infectious disease journal* 2009;28(1):21-4.
4. Holman RC, Curns AT, Belay ED, et al. Kawasaki syndrome in Hawaii. *The Pediatric infectious disease journal* 2005;24(5):429-33. [published Online First: 2005/05/07]
5. Burns JC, Herzog L, Fabri O, et al. Seasonality of Kawasaki disease: a global perspective. *PloS one* 2013;8(9):e74529. doi: 10.1371/journal.pone.0074529 [published Online First: 2013/09/24]
6. Rodo X, Curcoll R, Robinson M, et al. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. *Proceedings of the National Academy of Sciences of the United States of America* 2014;111(22):7952-7. doi: 10.1073/pnas.1400380111 [published Online First: 2014/05/21]

7. Ghelani SJ, Sable C, Wiedermann BL, et al. Increased incidence of incomplete kawasaki disease at a pediatric hospital after publication of the 2004 american heart association guidelines. *Pediatric cardiology* 2012;33(7):1097-103. doi: 10.1007/s00246-012-0232-9
8. Hall GC, Tulloh LE, Tulloh RM. Kawasaki disease incidence in children and adolescents: an observational study in primary care. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2016;66(645):e271-6. doi: 10.3399/bjgp16X684325 [published Online First: 2016/02/26]
9. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *The New England journal of medicine* 1986;315(6):341-7. doi: 10.1056/NEJM198608073150601
10. Chen KY, Curtis N, Dahdah N, et al. Kawasaki disease and cardiovascular risk: a comprehensive review of subclinical vascular changes in the longer term. *Acta paediatrica* 2016;105(7):752-61. doi: 10.1111/apa.13367 [published Online First: 2016/02/18]
11. Wardle AJ, Connolly GM, Seager MJ, et al. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane database of systematic reviews* 2017;1:CD011188. doi: 10.1002/14651858.CD011188.pub2 [published Online First: 2017/01/28]
12. Dhillon R, Newton L, Rudd PT, et al. Management of Kawasaki disease in the British Isles. *Archives of disease in childhood* 1993;69(6):631-6; discussion 37-8.
13. Holman RC, Belay ED, Curns AT, et al. Kawasaki syndrome hospitalizations among children in the United States, 1988-1997. *Pediatrics* 2003;111(2):448. [published Online First: 2003/02/04]
14. Chang RK. The incidence of Kawasaki disease in the United States did not increase between 1988 and 1997. *Pediatrics* 2003;111(5 Pt 1):1124-5.
15. Stockheim JA, Innocentini N, Shulman ST. Kawasaki disease in older children and adolescents. *The Journal of pediatrics* 2000;137(2):250-2. doi: 10.1067/mpd.2000.105150
16. Brogan PA, Bose A, Burgner D, et al. Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Archives of disease in childhood* 2002;86(4):286-90.
17. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004;110(17):2747-71. doi: 10.1161/01.CIR.0000145143.19711.78
18. ONS. 2011-2015 census. Ethnic group, local authorities in the United Kingdom". *Office of National Statistics* 2017
19. Central Statistics Office. Census 2011 small area population statistics (SAPS). Census Statistics Office. 2015 [cited 2015 November]. Available from: https://www.cso.ie/en/census/census2011smallareapopulationstatisticssaps/
20. Benseler SM, McCrindle BW, Silverman ED, et al. Infections and Kawasaki disease: implications for coronary artery outcome. *Pediatrics* 2005;116(6):e760-6. doi: 10.1542/peds.2005-0559
21. McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. *Circulation* 2007;116(2):174-9. doi: 10.1161/CIRCULATIONAHA.107.690875

22. 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 : official publication of the American Society of Echocardiography* 2011;24(1):60-74. doi: 10.1016/j.echo.2010.10.004
23. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017;135(17):e927-e99. doi: 10.1161/CIR.0000000000000484 [published Online First: 2017/03/31]
24. Kobayashi T, Inoue Y, Morikawa A. [Risk stratification and prediction of resistance to intravenous immunoglobulin in Kawasaki disease]. *Nihon rinsho Japanese journal of clinical medicine* 2008;66(2):332-7.
25. Davies S, Sutton N, Blackstock S, et al. Predicting IVIG resistance in UK Kawasaki disease. *Archives of disease in childhood* 2015;100(4):366-8. doi: 10.1136/archdischild-2014-307397 [published Online First: 2015/02/12]
26. Harnden A, Alves B, Sheikh A. Rising incidence of Kawasaki disease in England: analysis of hospital admission data. *Bmj* 2002;324(7351):1424-5.
27. Tizard EJ, Suzuki A, Levin M, et al. Clinical aspects of 100 patients with Kawasaki disease. *Archives of disease in childhood* 1991;66(2):185-8.
28. Mossberg M, Segelmark M, Kahn R, et al. Epidemiology of primary systemic vasculitis in children: a population-based study from southern Sweden. *Scandinavian journal of rheumatology* 2018:1-8. doi: 10.1080/03009742.2017.1412497 [published Online First: 2018/02/08]
29. Lyskina G, Bockeria O, Shirinsky O, et al. Cardiovascular outcomes following Kawasaki disease in Moscow, Russia: A single center experience. *Glob Cardiol Sci Pract* 2017;2017(3):e201723. doi: 10.21542/gcsp.2017.23 [published Online First: 2018/03/23]
30. Chen S, Dong Y, Kiuchi MG, et al. Coronary Artery Complication in Kawasaki Disease and the Importance of Early Intervention : A Systematic Review and Meta-analysis. *JAMA Pediatr* 2016;170(12):1156-63. doi: 10.1001/jamapediatrics.2016.2055 [published Online First: 2016/10/18]
31. Jakob A, Whelan J, Kordecki M, et al. Kawasaki Disease in Germany: A Prospective, Population-based Study Adjusted for Underreporting. *The Pediatric infectious disease journal* 2016;35(2):129-34. doi: 10.1097/INF.0000000000000953 [published Online First: 2015/10/16]