Kawasaki disease incidence in children and adolescents: an observational study in primary care

INTRODUCTION
Kawasaki disease is an acute systemic vasculitis of unknown cause. The epidemic nature and high rates in siblings support an infectious agent inducing the disease in genetically susceptible individuals. Kawasaki disease is characterised by a persistent fever; bilateral non-exudative conjunctivitis; erythema of the lips and oral mucosa; changes in the extremities; rash; and cervical lymphadenopathy. Disease definitions require a fever for 5 days plus four of the five remaining criteria in the North American guidelines, or five of the six symptoms in Japan. Incomplete cases have fewer characteristics, whereas atypical Kawasaki disease generally includes only two or three of the criteria plus coronary artery aneurysms. Coronary artery aneurysms or ectasia develop in 15–25% of untreated children but early treatment with intravenous immunoglobulin and aspirin reduces the occurrence to about 4.5%. Recently published guidelines also recommend the use of steroids, for high-risk cases and in those who fail to respond to intravenous immunoglobulin, with continued aspirin therapy and cardiovascular monitoring after discharge.

A study of English Hospital Inpatient Statistics (1991–2003) reported an increase in Kawasaki disease in children aged <5 years and cases have been reported after certain childhood vaccinations. Knowledge of the current background rate is important, for example, in post-marketing surveillance of new immunisations, when observed to expected rates may be compared.

This study was designed to update figures on the UK incidence of Kawasaki disease, and the temporal and seasonal trends, and to extend this across a wider age range. Methods for case identification from electronic primary healthcare records were also investigated.

METHOD
This was a retrospective, descriptive, observational study. The source population, diagnoses, and patient characteristics were identified from The Health Improvement Network (THIN) database of electronic primary healthcare records from practices throughout the UK. Details of demographics, primary care diagnoses, and prescription treatment are routinely recorded against the date within individual patient records. Secondary care diagnoses and deaths are also captured because of the UK healthcare system where primary care physicians act as ‘gatekeepers’ to secondary care and must be informed of diagnoses, treatment, or monitoring. Events automatically coded at entry using the Read system can be supplemented with unstructured text including electronic discharge summaries. THIN has been shown to be generalisable to the UK population for demographics, major condition prevalence, and death rates; and similar in terms of deprivation, although with slightly fewer people aged <20 years compared with the general UK population.

Abstract

Background
Kawasaki disease is reported to be increasing in incidence and is the commonest childhood cause of acquired heart disease in the Western world.

Aim
To determine the current UK incidence of Kawasaki disease across childhood and adolescence; and investigate trends over time and season.

Design and setting
An observational, descriptive study in the UK.

Method
The Health Improvement Network (THIN) database of primary healthcare records was searched for codes or text indicating Kawasaki disease. Identified records were compared with a study case definition and a date of onset was assigned to cases. The incidence, age/sex distribution, and trend in seasonal and temporal distribution were estimated (2008–2012).

Results
A total of 110 episodes of Kawasaki disease in 109 children were identified from 3.9 million person-years observation. The incidence of Kawasaki disease was 2.8 per 100 000 person-years (95% confidence interval [CI] = 2.3 to 3.4) when aged <20 years; 9.1 (95% CI = 7.3 to 11.2) aged <5 years, and 3.0 per 100 000 (95% CI = 2.0 to 4.3) across the age groups when possible cases were included. More cases were identified in males (55%) with one-fifth of cases diagnosed after 5 years of age. There was no statistically significant trend in incidence over the study years (P= 0.10 adjusted for sex and month), or between seasons (P= 0.65 adjusted for year and sex).

Conclusion
Although the incidence of Kawasaki disease remains low and has stabilised in the UK, GPs should recognise that the condition occurs throughout childhood and across the seasons.

Keywords
adolescents; children; epidemiology; incidence; Kawasaki disease.
How this fits in

The UK incidence of Kawasaki disease has been reported to 2003 for those <5 years of age and was increasing at that time. A current UK incidence for Kawasaki disease is reported which shows that levels stabilised between 2008 and 2012. Although the incidence is highest in those aged <5 years, the wider age group studied showed that one-fifth of cases occurred in older children, one after 15 years of age. A search strategy was developed for use in future studies, based on electronic primary healthcare records.

Case identification

The study population comprised 1.29 million people permanently registered at one of 472 THIN practices any time between 2008 and 2012 inclusive when they were <20 years of age. THIN includes the month of birth for children up to the age of 15 and the year of birth for older people. Date of birth was assumed to be the 16th of their month of birth for those <10 years of age and 30 June of their year of birth for older people.

Searches identified any patient records with a code for Kawasaki disease or ‘Kawasaki’ text (a supplementary file of search codes and terms is available from the authors). The search period was defined for each child as between the most recent of 1 January 2008, 1st of the child’s month of birth, or transfer from another practice plus 6 months and the earliest of 31 March 2012, transfer out of the practice, last data collection, or age 20 years and 90 days. Exclusion of 6 months after registration allowed the recording of historical cases, whereas searches for 3 months after the study end captured cases with onset during the study period but a later diagnosis.

Identified records were reviewed independently by two of the authors who classified the event as an incident episode, or not, against a case definition, and assigned a date of onset. If there was insufficient information to form a decision then the practice was contacted and asked for further information (n = 134 requests). All authors agreed on the classification and date as a group if there was a lack of consensus. Retrieval of unstructured text and practice documents used an established system via a third party, which required removal of all potentially identifying details before any information is passed to researchers.

Cases were those with a documented final secondary care diagnosis of Kawasaki disease. The accuracy of the diagnosis was not judged if the full secondary care notes were not available. When it was not clear that the diagnosis had been made in secondary care, then a record of a diagnosis in the primary care record [not a primary care diagnosis] was accepted if this was supported by evidence of a diagnosis of a coronary aneurysm or concomitant initiation of aspirin therapy, or monitoring for a coronary artery aneurysm. Onset was the date that the fever started or, if this was not recorded, the date of the first clinical characteristic of Kawasaki disease. If these details were not recorded then onset was assumed to be the date of diagnosis.

The review process identified records with a final secondary care discharge diagnosis of possible Kawasaki disease. A sensitivity analysis included a possible category defined as a final secondary care diagnosis of ‘?’ or ‘suspected’ Kawasaki disease (or similar), or a diagnosis of Kawasaki disease in the primary care record with a record of fever for at least 5 days and three principal characteristics of the condition immediately prior to the diagnosis and not included in the full Kawasaki disease category.

Additional searches

To identify false negatives, the searches were repeated looking for Kawasaki disease sequelae, treatment, or alternative terms (a supplementary file of search codes and terms is available from the authors) and records were reviewed for an alternative explanation. Codes for coronary aneurysm, or codes and terms for acute febrile mucocutaneous lymph node syndrome, polyarteritis nodosa, and hydrops of bladder [total n = 121] were included. Further searches identified aspirin prescriptions without a code from a list of alternative indications (n = 1249), and records with the text ‘aneurysm’ [a sample of 328, 26% reviewed]. Aspirin is contraindicated in most children because of potential Reye’s syndrome so can be a marker for Kawasaki disease. As there was no Read Code for coronary artery aneurysm and false negatives were being sought, more general codes were used.

Statistical analysis

Kawasaki disease episodes were included when onset was dated 2008–2012 inclusive, before the age of 20, and 6 months after transfer from another practice. Person-years at-risk between these dates were calculated for the study population in total, for each season [December to February, March to May, and so on across years], calendar year, and within age/sex groups.
and the incidence calculated with 95% confidence intervals (CI). A sensitivity analysis included cases categorised as possible Kawasaki disease.

To test whether there were significant differences between years and seasons, generalised linear model analysis of variances (GLM ANOVAs) were performed on the variance stabilising square root transformation of the incidence rates. The square root transformation was used, as the data followed a Poisson distribution that violates the normality assumption of ANOVA. As none of the effects were statistically significant at the 95% significance level ($P = 0.05$), no pairwise tests for differences between individual means were performed.

The positive predictive value (PPV) and sensitivity of a Kawasaki disease code were estimated.

### RESULTS

The analysis included 110 episodes of Kawasaki disease in 109 children from 3.9 million person-years at risk.

The annual incidence of Kawasaki disease per 100,000 people varied by age and sex (Table 1). The incidence was highest in the first year of life, with a peak incidence of 14.6 per 100,000 person-years in the 6-12 months age group. The incidence decreased with age, with the lowest incidence observed in children aged 15-19 years (0.1 per 100,000 person-years).

The distribution of Kawasaki disease by year of onset is shown in Figure 1. The incidence remained relatively stable over the study period, with a slight increase observed in 2011.

The distribution of Kawasaki disease by season of onset is shown in Figure 2. The highest incidence was observed in the spring, followed by the summer and autumn, with the lowest incidence in the winter.

The median age at onset was 3 years and 4 months (range 2 months–15 years 1 month; interquartile range 1 year 9 months–4 years 6 months). There were differences in age distribution between the sexes; however, the numbers in each group were too small and the CIs too wide (Table 1) to allow a meaningful comparison.

There was no statistically significant trend in incidence over the study years ($P = 0.1$ adjusted for sex and month) (Figure 1), or between seasons ($P = 0.65$ adjusted for year and sex) (Figure 2).

Inclusion of a further eight cases categorised as possible Kawasaki disease increased the annual incidence to 3.0 per 100,000 (95% CI = 2.3 to 3.8). The median

<table>
<thead>
<tr>
<th>Age-sex group</th>
<th>Person-years</th>
<th>Incidence (95% CI)</th>
<th>Person-years</th>
<th>Incidence (95% CI)</th>
<th>Person-years</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3,900,807</td>
<td>2.8 (2.3 to 3.4)</td>
<td>1,891,621</td>
<td>2.6 (2.0 to 3.5)</td>
<td>2,009,187</td>
<td>3.0 (2.3 to 3.8)</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>76,395</td>
<td>6.5 (2.7 to 15.7)</td>
<td>37,293</td>
<td>8.0 (2.6 to 24.9)</td>
<td>39,102</td>
<td>5.1 (1.3 to 20.5)</td>
</tr>
<tr>
<td>6-12 months</td>
<td>92,149</td>
<td>11.9 (6.6 to 21.6)</td>
<td>45,006</td>
<td>8.9 (3.3 to 23.7)</td>
<td>47,143</td>
<td>14.8 (7.1 to 31.1)</td>
</tr>
<tr>
<td>12-18 months</td>
<td>100,659</td>
<td>5.0 (2.1 to 11.9)</td>
<td>49,156</td>
<td>8.1 (3.1 to 21.7)</td>
<td>51,502</td>
<td>1.9 (0.3 to 13.8)</td>
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<tr>
<td>19-24 months</td>
<td>101,388</td>
<td>7.9 (3.9 to 15.8)</td>
<td>49,480</td>
<td>6.1 (2.0 to 18.6)</td>
<td>51,908</td>
<td>9.6 (4.0 to 23.1)</td>
</tr>
<tr>
<td>24-36 months</td>
<td>201,898</td>
<td>9.9 (6.4 to 15.4)</td>
<td>98,607</td>
<td>10.1 (5.5 to 18.8)</td>
<td>103,291</td>
<td>9.7 (5.2 to 18.0)</td>
</tr>
<tr>
<td>36-48 months</td>
<td>200,693</td>
<td>12.0 (8.0 to 17.8)</td>
<td>98,012</td>
<td>7.1 (3.4 to 15.0)</td>
<td>102,680</td>
<td>16.6 (10.3 to 26.6)</td>
</tr>
<tr>
<td>48-50 months</td>
<td>198,819</td>
<td>7.5 (4.5 to 12.5)</td>
<td>97,245</td>
<td>9.3 (4.8 to 17.8)</td>
<td>101,574</td>
<td>5.9 (2.7 to 13.1)</td>
</tr>
<tr>
<td>5-9 years</td>
<td>959,112</td>
<td>2.2 (1.4 to 3.4)</td>
<td>468,702</td>
<td>2.1 (1.1 to 4.0)</td>
<td>490,410</td>
<td>2.2 (1.2 to 4.1)</td>
</tr>
<tr>
<td>10-14 years</td>
<td>993,333</td>
<td></td>
<td>484,837</td>
<td></td>
<td>508,497</td>
<td></td>
</tr>
<tr>
<td>15-19 years</td>
<td>976,361</td>
<td>0.1 (0.0 to 0.7)</td>
<td>463,282</td>
<td></td>
<td>513,079</td>
<td>0.2 (0.0 to 1.4)</td>
</tr>
</tbody>
</table>
age at onset remained at 3.4 years and the ratio of incidence in males to females was 1.1:1.

Ninety-seven episodes of Kawasaki disease in 96 children and two possible episodes were identified from 117 records with a Kawasaki disease code, between 2008 and 2012. The remaining 13 episodes and six possible episodes were identified from 725 records with a ‘Kawasaki’ text entry. No episodes of Kawasaki disease were identified from the search of records with sequelae, treatment, or alternative terms. The PPV of a Kawasaki disease code during the study period was therefore 82%; sensitivity 88%. Both PPV and sensitivity were 84% when possible cases were included.

**DISCUSSION**

**Summary**

The incidence of Kawasaki disease has stabilised and remains small at 2.8 per 100 000 population <20 years of age. A slight upward trend in rate between 2008 and 2012 was not statistically significant. Although the majority of cases were in those <5 years of age, the age group in the previous UK study, one-fifth of cases were identified in older patients, including one >15 years of age. Inclusion of possible cases increased the annual incidence slightly to 3.0 per 100 000 population <20 years, with little change in the median age and sex distribution.

**Strengths and limitations**

This data source allowed the inclusion of patients seen at all types of secondary care units across the UK rather than being biased towards specialist centres, and allowed identification of second episodes without double counting of readmissions that can occur within hospital statistics. It is unlikely that a primary care practice would be unaware of a diagnosis of Kawasaki disease given the UK healthcare system, where the GP is informed of the initial diagnosis as well as any follow-up, and has the responsibility for ongoing prescription treatment. The finding that no additional cases were found from focused searches of records with aspirin, sequelae, or alternative terms is reassuring, adding confidence in the completeness of case ascertainment. This will allow simplification of searches in future studies. The search of text entries in the electronic records identified 12% of episodes, so is needed to maximise case ascertainment. Most text entries noted that a diagnosis had been ruled out. Those records with a Kawasaki disease code not adjudicated as an episode generally referred to monitoring of historical cases and this finding highlights the difficulty in ascertaining new episodes of acute conditions from electronic healthcare records.

Undiagnosed cases could not be identified using these data. If cases were missed, there is potential for bias, for example, if Kawasaki disease is considered more often in younger children. Slight under-representation of those aged <20 years on THIN may have resulted in bias if this was due to low registration of particular ethnic groups, as Kawasaki disease is more common in some Asian populations. The lack of detailed secondary clinical notes in primary care records meant that it was not feasible to understand whether possible episodes were incomplete cases or to estimate the ratio of complete to incomplete cases. Despite the 3.9 million person-years studied, confidence intervals on the incidence estimates are wide for some results.

**Comparison with existing literature**

Previous studies of admissions for Kawasaki disease in England in children aged <5 years have reported an annual incidence of 8.4 per 100 000 (1998–2003) and an increase from 4.0 to 8.1 per 100 000 between 1991–1992 and 1999–2000. The current incidence of 9.1 per 100 000 in this age group, along with no statistical trend over the study period, suggests that levels have stabilised. The earlier incidence is well within the 95% CIs for this study, whereas a continued doubling of annual incidence or an increase of 4.1 per 100 000 population in the decade between studies to 16.2 or 12.2 per 100 000 population, respectively, is above the upper confidence interval. It is possible that the earlier trend in incidence reflected an improvement in diagnosis rather than an increase in the actual rate of disease. Danish data showed an increase in incidence from 1981 to 1999, which then stabilised to 2004, while no trend in incidence was reported from Finland, Norway, or Sweden between 1999 and 2009, or between 2008 and 2012 in the Netherlands. The incidence of Kawasaki disease has continued to increase in Japan from the higher starting level seen in many Asian countries.

Other Northern European countries have reported annual incidences for those <5 years of age between 4.5 and 11.4 per 100 000 population. The age distribution also differs. In Denmark, the distribution was similar to that in the current study, with
the highest incidence at age 4–6 months and then in the second and third years of life,\textsuperscript{11} whereas Dutch data showed the highest number of cases in the first year, with a drop thereafter.\textsuperscript{15} Other authors have reported a slight preponderance of Kawasaki disease in boys\textsuperscript{12,14,15} and the majority of cases before a child’s 5th birthday\textsuperscript{12–15} but with cases into the teenage years reported when this group was studied.\textsuperscript{15}

The seasonal variation in onset of Kawasaki disease is of interest, as the condition may be due to one or more infectious agents, or to pollen in allergic individuals.\textsuperscript{1,18} A meta-analysis of studies from the northern hemisphere extra-tropical latitudes reported that case numbers were highest in January through to March and lowest from August through to October.\textsuperscript{19} Although this is roughly consistent with the current data, no statistically significant trend across the seasons has highlighted that Kawasaki disease can occur at any time of year.

**Implications for practice**

Although the incidence of Kawasaki disease is not increasing in the UK and remains small, GPs should be aware that the condition occurs throughout childhood and across the seasons. Given the potential cardiovascular sequelae, the condition should be considered in children with persistent fever, even in older children when the absolute risk is lower. The discharge diagnoses of possible Kawasaki disease may suggest that secondary care centres are not always confident when diagnosing the condition and highlights the need for the proposed diagnostic marker.\textsuperscript{20}

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**Funding**

The study was funded by Novartis Vaccines and Diagnostics through Cegedim Strategic Data (CSD), without restriction on publication.

**Ethical approval**

The study was approved by THIN Scientific Research Committee: SRC Reference Number 13-044.

**Provenance**

Freely submitted; externally peer reviewed.

**Competing interests**

Gillian Hall is on the Advisory Committee of the THIN database and has received funding for research and consultancy from a number of pharmaceutical companies and from charities. All other authors have no competing interests to report.

**Acknowledgements**

The authors thank Fiona Hill and her colleagues at CSD, Katy Munro, Dirk van Schalkwyk, and the GPs and staff at all practices that contribute data to the THIN database.

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