Kawasaki Disease in Germany

A Prospective, Population-based Study Adjusted for Underreporting

André Jakob, MD, Jane Whelan, MD, PhD, MPH,† Matthaeus Kordecki,* Reinhard Berner, MD,‡ Brigitte Stiller, MD,* Raoul Arnold, MD,§ Rudiger von Kries, MD,¶ Elena Neumann,* Nicholas Roubinis, MSc,† Mirna Robert, MD, MPH,† Jochen Grohmann, MD,* René Höhn, MD,* and Markus Hufnagel, MD‖*

Background: National estimates of Kawasaki disease (KD) incidence often do not include incomplete cases (diagnosed based on only laboratory or echocardiographic criteria), and/or they rely on retrospective case reports and data registries where underreporting is known to be a problem.

Methods: We conducted a prospective nationwide KD surveillance study in children younger than 5 years through the hospital-based German Pediatric Surveillance Unit (ESPED). We accounted for underreporting through applying capture–recapture methodology in 2 federal states using hospital discharge records with KD International Statistical Classification of Diseases and Related Health Problems 10th revision code (ie, M30.3). KD diagnosis (complete and incomplete) was established according to the American Heart Association criteria, 2004.

Results: Incidence of KD, corrected for underreporting, was 7.2 of 100,000 in children younger than 5 years in Germany. Underreporting to ESPED was estimated at 37%–44%. Overall, 315 validated KD cases were reported. Of the 64 (20%) incomplete cases, 58% (37/64) were detected through echocardiographic findings and 42% (27/64) through laboratory criteria alone. Incomplete cases were younger than complete cases (1.2 vs. 2.0 years, $P = 0.0001$) and had more coronary aneurysms (43% vs. 11%, $P = 0.0001$).

Conclusions: A substantial number of incomplete KD cases were diagnosed based on the laboratory and echocardiographic criteria only. This was particularly the case in relation to infants younger than 1 year—an age group known to have an increased risk of developing coronary aneurysms. In addition, we found a high rate of underreporting to national Pediatric Surveillance Units. We suggest that improved surveillance and development of better diagnostic tests remain a high priority.

Key Words: Kawasaki disease, epidemiology, incidence, Germany

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Kawasaki disease (KD) is the most common form of generalized vasculitis in children younger than 5 years. The etiology is unknown, and no specific diagnostic test exists thus far. KD was first described in Japan in the 1960s,[1] and the first case in Germany was reported in 1979.[2] Because of its effect on coronary arteries, KD results in substantial morbidity and mortality. In the United States and Japan, it is considered the most common cause of acquired heart disease in children.[3,4]

The diagnostic criteria originally described in Japan evolved because it was increasingly recognized that the "classical" clinical case definition was inadequate for KD diagnosis in young children.[5] This led to underdiagnosis of KD and children who could otherwise have benefitted from treatment were missed. Historically, the reported incidence was also underestimated because these cases (known as "incomplete" KD cases) were not included in the estimates.

Annual incidence varies geographically and by ethnic background. Since KD was first described, Japan [which has the highest reported annual rate on a global basis (239 per 100,000 in 2010)][6] has witnessed a continuous increase in incidence rates, well documented through 21 serial nationwide surveys. Similar increases have been observed in neighboring Taiwan.[7] In regions of predominantly European Caucasian racial background, the reported incidence is lower although it varies considerably between countries and over time. Rates in children younger than 5 years in the United States (20.8 per 100,000 in 2006)[8] and Canada (26.2 per 100,000 in 2006)[9] exceed those in Europe, Australia, New Zealand and Chile, where reported incidence rates range from 3.6 to 15.2 per 100,000.[10–19] Consistent seasonal fluctuations in temperate latitudes of the Northern Hemisphere (peaking in winter) have been described. This suggests a seasonal exposure, varying over wide geographic areas.[20]

Ultimately, the factors influencing recent global trends are uncertain, but they may in part be attributable to increased physician awareness, a more sensitive case definition, and improved diagnostics.[12,21] Most epidemiologic studies on KD rely on retrospective case reports and disease registries that suffer from well-recognized limitations, including incomplete data entry and underreporting.[10] In Germany, we conducted a prospective nationwide KD surveillance and adjusted for case underreporting using capture–recapture (CRC) methodology. We describe the epidemiology, seasonal and geographic variation, and clinical and laboratory characteristics of KD in children younger than 5 years.

MATERIALS AND METHODS

Study Design and Case Definition

Prospective, national surveillance was conducted between January 1, 2011, and December 31, 2012. Experience with national surveillance suggests that there is considerable underreporting,[21,22] so to account for this, we cross-validated the national surveillance data with hospital record data in a CRC analysis conducted in 2 German states, as described later. This study included all cases of KD diagnosed in Germany in children younger than 5 years treated

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From the *Department of Congenital Heart Defects, Heart Center University of Freiburg, Freiburg, Germany; †Novartis Pharma BV, Amsterdam, The Netherlands; ‡Clinic and Polyclinic for Pediatrics and Adolescent Medicine, University Children's Hospital, Technische Universität Dresden, Dresden, Germany; §Department of Pediatric Cardiology, University Hospital Heidelberg, Heidelberg, Germany; ¶Division of Epidemiology, Institute of Social Pediatrics and Adolescent Medicine, Ludwig-Maximilian's University Munich, München, Germany; and ‖Section of Pediatric Infectious Diseases and Rheumatology, Center for Pediatrics and Adolescent Medicine, University Medical Center Freiburg, Freiburg, Germany.

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Address for correspondence: André Jakob, MD, Universitäts Herzzentrum Freiburg-Bad Krozingen, Klinik für Angeborene Herzfehler, Mathildenstraße 1, 79106 Freiburg, Germany. E-mail: andre.jakob@universitaets-herzzentrum.de.

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with intravenous immune gamma globulin (IVIG) to avoid over-reporting of infants with suspected KD. Diagnoses were classified as complete or incomplete according to the American Heart Association guidelines.[23] Complete cases included those with persistent fever (≥5 days or fever for <5 days if it did not persist post-IVIG treatment) and with ≥4 of the principal clinical features [ie, (1) changes in extremities, such as erythema and edema of hands and feet, or desquamation of fingertips; (2) polymorphous exanthema; (3) bilateral conjunctivitis without exudate; (4) changes in the lips and oral cavity and (5) cervical lymphadenopathy].

Incomplete cases included those with fever and <4 clinical features with detection of coronary artery aneurysms (CAAs) or dilatation or those with laboratory evidence of systemic inflammation (C-reactive protein ≥30 mg/L) in combination with at least 3 other abnormal supplemental laboratory findings, namely (1) increased alanine transaminase, (2) albumin ≤3.0 g/dL, (3) leukocyturia, (4) anemia for age, (5) leukocytosis (≥15,000/mm^3) and (6) thrombocytosis (≥450,000/mm^3). CAA was diagnosed according to the Japanese Ministry of Health criteria for aneurysms as a lumen >3 mm in children younger than 5 years or a diameter 1.5 times the size of the surrounding segment or a clearly irregular lumen.[24] The Japanese criteria were used in preference to the coronary artery–specific Z score as they were better known and well established in Germany at the time of the study. Cases were excluded if their treatment did not include IVIG or they did not otherwise meet the case definition.

Data Sources

National Surveillance: German Pediatric Surveillance Unit (ESPED)

KD cases were identified nationally through the hospital-based German Pediatric Surveillance Unit (ESPED).[25] Data on rare pediatric diseases are actively collected from all children's hospitals, pediatric departments and departments of pediatric surgery (n = 423) on a monthly basis. KD was introduced to the register for the purposes of the study, announced in the journal of the *German Society of Pediatrics* (monthly publication) in advance of the study, and all participating hospitals were informed by letter. The diagnosis was established by the reporting physician who was sent a standardized questionnaire to provide clinical information, laboratory and echocardiographic findings. Reported KD cases were independently reviewed and validated by an adjudicating committee including a pediatric cardiologist (B.S.), a pediatric rheumatologist (M.H.) and a specialist in pediatric infectious disease (R.B.)

Regional Surveillance: Hospital Records From Baden Württemberg and Saxony

To determine the degree of KD underreporting to ESPED, cases were cross-validated against hospital discharge records using the KD International Statistical Classification of Diseases and Related Health Problems 10th revision code (ie, M30.3). Records were assessed retrospectively in all pediatric hospitals in 2 geographically distant states from the north-east and the south-west of Germany: Baden Württemberg (BW; total population: 10,569,111) and Saxony (population: 4,050,204). These states together account for 18% of the total population in Germany and are representative of the national population in terms of age distribution and ethnic makeup (based on the self-reported nationality in the 2011 census).

Population Data

Population denominator data, population density per square kilometer, proportion of land under farming and proportion of high-risk ethnic groups resident in the federal state were extracted from the Federal Statistics Office database (https://www.destatis.de/).

Statistical Analysis

Differences between proportions were tested using Pearson χ^2 or Fischer exact test, and between means using 2-sided independent sample *t* tests. Logistic regression was used to estimate the relationship between laboratory findings and age group (age < 1 year vs. age ≥ 1 year). The outcome is reported as an odds ratio (OR) with 95% confidence interval (CI). Incidence rates were estimated as the annual number of reports of KD per 100,000 children younger than 5 years in Germany, corrected for case under-ascertainment in ESPED using a 2-source CRC method.[26,27]

Capture–Recapture

KD cases residing in Saxony or BW were included in the CRC estimate. The principle assumptions of CRC are[26] as follows: (1) perfect case linkage between sources; (2) the same catchment probability between individuals; (3) independence between sources; (4) a closed study population. Hospital cases were linked with ESPED reports using 5 variables: hospital number, age at onset of illness, gender, month/year of admission and the first 3 digits of the residential postal code. Where cases were detected through hospital surveillance, but not reported to ESPED, the treating physician was contacted to complete an identical ESPED questionnaire. To account for possible heterogeneities in capture probabilities (ie, that some subgroups of the population are more or less likely to be recorded than others), we present the Chapman CRC estimator stratified by age and gender.[26–28] To validate our stratified CRC estimate, we also report Chao lower bound estimator (including CIs),[27,29] which relaxes the assumption that sources are independent.

Spatiotemporal Characteristics of Cases

Seasonal variation was examined using ordinary regression to fit a sine curve to the time series of weighted monthly case counts. The outcome is reported as a peak-to-trough ratio, comparing the months of highest and lowest incidence.[30,31] The regional distribution of cases was summarized by federal state for ESPED reports only (Fig. 1). Regional incidence was compared with the ESPED national incidence using Poisson regression analysis. The rate ratio is reported as a standardized morbidity ratio (SMR) with a 95% CI.

RESULTS

National Surveillance Through ESPED

Nationwide, 338 children younger than 5 years were reported to ESPED during 2011 and 2012. Three hundred and one cases remained for evaluation after exclusion of 14 duplicate records, 11 cases that were not treated with IVIG, 4 children without permanent German residence and 8 children for whom KD diagnosis later was canceled. On further review, an additional 29 cases (9.6%) did not meet the case definition despite treatment with IVIG and were excluded. Of 272 validated cases identified, 122 were hospitalized in 2011 and 150 in 2012. Mean age was 1.9 years (standard deviation: 1.4) and 66.1% (179 of 271) were male. Overall, 79.8% (217 of 272) were classified as complete KD cases and 20.2% (55 of 272) as incomplete cases. Of the incomplete cases, 58.2% (32 of 55) were echocardiographic positive and 41.8% (23 of 55) were positive by laboratory findings. ESPED reports in BW and Saxony accounted for 14.3% of cases nationally (39 of 272). There was no difference in the age distribution nationally or in either of the 2 states surveyed, but in Saxony,

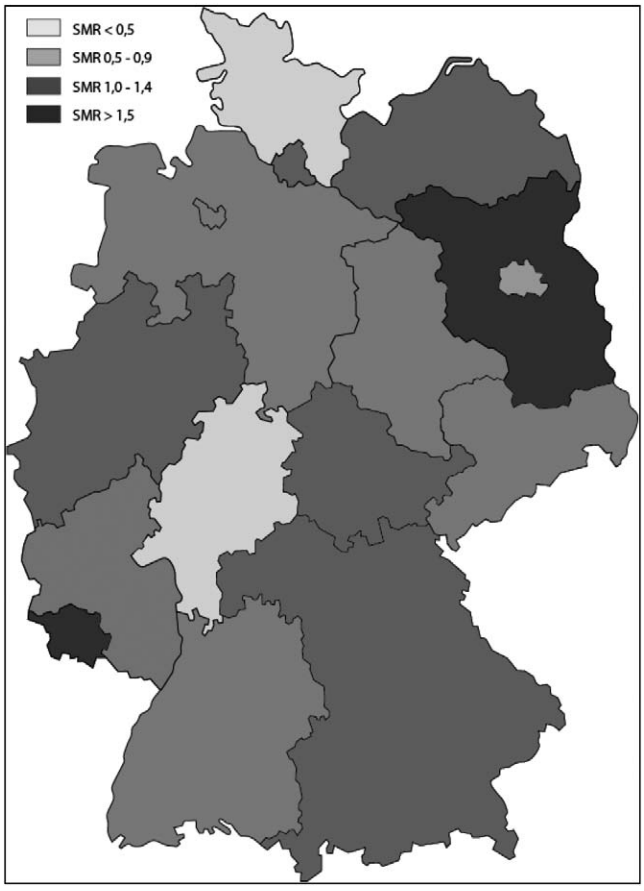

FIGURE 1. Spatial distribution of KD cases in children younger than 5 years in Germany from 2011 to 2012. Patient's residence was assigned using the first 3 digits of the patient's postcode (to protect anonymity, only an abbreviated postcode is recorded for cases). Some 3-digit postcodes may correspond to more than 1 state and the 5-digit postcode of the hospital attended. If both codes were compatible, it was assumed that the patient was resident in that state. Where there were differences at the state level between where the patient was hospitalized and their home postcode (n = 3), cases were omitted from the regional analysis. By using ESPED reports only, the SMR in 2 regions exceeded the national mean (4.0/100,000, 95% CI: 3.6–4.5, as a reference) in 2011/2012: Brandenburg (SMRref: 2.3, 95% CI: 1.4–3.7) and Bavaria (SMRref: 1.4, 95% CI: 1.1–1.9). The SMR in Hessen was lower than the national mean (SMRref: 0.4, 95% CI: 0.2–0.8).

there was a trend toward more female cases (7 of 11, 63.6%) compared with BW (12 of 28, 42.9%) or other regions nationally (73 of 232, 31.5%; Pearson χ^2 test: 5.95, $P = 0.055$).

Regional Surveillance: Hospital Records in BW and Saxony

Of the 65 hospitals invited to participate in BW and Saxony, the response rate was 97% (63 of 65). Hospital surveillance identified 89 children with KD during the study period, of whom 4 were nonresident in BW or Saxony, and 10 did not meet the inclusion criteria. Of the remaining 75 records, 36 were also notified in ESPED, whereas 39 cases were notified through hospital records only. The latter were classified as complete KD (n = 31) and incomplete (n = 8, 5 of which were echocardiographic positive and 3 met laboratory criteria only). There was no difference in the age or gender distribution of cases notified through hospital records.

Incidence in Germany

Cases classified according to the American Heart Association algorithm were included in the CRC incidence estimate (n = 39 ESPED and n = 75 hospital records). The true number of cases and corresponding incidence rates according to the Chapman estimate and the Chao lower bound estimate are reported by age and gender in Table 1. These estimates yield an overall incidence of 6.4 per 100,000 (95% CI: 6.2–7.2; ie, Chapman estimate) and 7.2 per 100,000 (95% CI: 6.4–10.1; ie, Chao estimate), respectively, in children younger than 5 years. This translates into point estimates of 435 and 489 cases nationally in children younger than 5 years during the study period, an underestimate of the true incidence of 37%–44%.

Clinical Characteristics of KD Cases

Nationally, 315 cases were identified through ESPED and/or hospital surveillance. Incomplete KD cases accounted for 20.3% of cases (n = 64/315), of which 42.2% (n = 27/64) were diagnosed based on the laboratory criteria only. Younger children were more likely to present with incomplete KD than older children [mean age, 2.0 years (complete) vs. 1.2 years (incomplete, $t = -4.06$, $P < 0.001$)]. Of children younger than 1 year (n = 76), 19.7% (15 of 76) were diagnosed on the basis of a positive echocardiogram and 23.7% (18 of 76) on laboratory findings only, compared with 9.2% (22 of 239) and 3.8% (9 of 239) in children older than 1 year, respectively. Children younger than 1 year were more likely to have leukocytosis (OR: 2.4; 95% CI: 1.4–4.0; $P = 0.002$) and thrombocytosis (OR: 3.1; 95% CI: 1.7–5.9, $P < 0.001$) than children older than 1 year. There were high rates of anemia in children younger than 6 months (73.0%, 27 of 37), but this proportion did not differ significantly from older children (ie, 63.2%, 151 of 239) or children aged 6 months to 1 year (58.9%, 23 of 39), $P = 0.410$. Among all cases, risk factors associated with the development of CAAs were (1) young age (<1 year), (2) male gender and (3) delayed treatment with IVIG. Children with CAA were more likely to have received repeat IVIG treatment (Table 2). Of cases that did not meet the inclusion criteria (n = 34 in total), 24 had 2 or 3 clinical signs but no additional laboratory or echocardiographic findings allowing them to be defined as incomplete cases. A higher proportion of children older than 1 year did not meet the case definition (12.1%, 33/272) than children younger than 1 year (1.3%, 1 of 77; Pearson χ^2 (1 df) = 8.0, $P = 0.005$).

Spatiotemporal Distribution

There was a clear seasonal distribution of cases (Fig. 2), with the peak of cases occurring on January 22 and a peak-to-trough ratio of 1.6 (95% CI: 1.1–2.2). Cases were widely distributed nationally (Fig. 1). By using ESPED reports only, the SMR in 2 states significantly exceeded the national mean (4.0 of 100,000, 95% CI: 3.5–4.5, as a reference) in 2011 to 2012: Brandenburg (SMR_{ref}: 2.3; 95% CI: 1.4–3.7) and Bavaria (SMR_{ref}: 1.4; 95% CI: 1.1–1.9). The SMR in Hessen was lower than the national mean (SMR_{ref}: 0.4; 95% CI: 0.2–0.7; Fig. 1). Twelve clusters of ≥3 cases in the same 3-digit postal code area were reported across 5 states. Five of these clusters (18 cases) were reported in Bavaria and 2 clusters (6 cases) in Brandenburg. No correlation was found among incidence rates by state and state population density per square

TABLE 1. Incidence Rates for KD Cases Younger Than 5 Years in Germany, 2011 to 2012

					CRC Estimates			
					Estimated True Cases		Incidence in BW and Saxony (Rate/100,000 Population <5 yr*)	
	ESPED Reports (n1)	Hospital Surveillance (n2)	ESPED + Hospital Reports (Overlap) (m)	Total Unique Cases Observed (N_O)	N_{Chap}	95% CI†	IR	Range
Chapman estimator‡								
Crude annual incidence	39	75	36	78	81	79–91	6.4	6.2–7.2
Age (yr) at hospitalization								
0	12	22	12	22	22	—§	8.8	
1	8	21	8	21	21		8.4	
2	9	12	7	14	15	14–22	5.9	4.5–10.9
3	3	10	2	11	14	11–28	5.5	4.5–10.8
4	7	10	7	10	10		3.9	
Stratified total	*39*	*75*	*36*	*78*	*82*			
Gender								
Male	20	40	17	43	47	44–58	7.3	6.8–9.0
Female	19	35	19	35	35		5.7	
Stratified total	*39*	*75*	*36*	*78*	*82*			
Chao estimator¶	39	75	36	78	90	81–127	7.2	6.4–10.1

*Denominator is mid-year population estimate in children younger than 5 years in Germany, 2011 and 2012 (Destatis).
†CIs throughout as recommended by Chao.[29]
‡Chapman estimator and variance as recommended by Brittain and Böhning.[27]
§Zero cases were unique to the ESPED data set. 95% CI could not be estimated because of null variance.
¶Chao estimator and variance as recommended by Chao.[29]

kilometer, proportion of land under farming or proportion of high-risk ethnic groups resident in the region (data not shown).

DISCUSSION

The diagnosis of KD is complex, and the appearance of its classical clinical signs may not be enough to secure a diagnosis. Many national estimates of KD incidence are based on the retrospective case reports or on registries that do not take account of cases diagnosed with the aid of laboratory and/or echocardiographic test results. Without this supplemental information, incomplete cases will be missed and the true incidence underreported.[10] In our study, we account for both: incomplete cases using laboratory and echocardiographic findings and underreporting by applying CRC methodology, which allows us to estimate a more realistic range of KD incidence. Depending on the CRC method employed, the incidence in Germany in children younger than 5 years treated with IVIG ranged from 6.4 of 100,000 to 7.2 of 100,000. Underreporting to our primary data source, the national Pediatric Surveillance Unit (ESPED; ref. Website: www.inopsu.com/countries) is known to be high.[24,25] To account for this, we supplemented ESPED data with active hospital surveillance in 2 German states (18% of the German population). By using the well-known Chapman estimator,[27,28] we obtained a crude estimate

TABLE 2. Risk Factors for Coronary Artery Aneurysm in KD Patients Younger Than 5 Years in Germany, 2011 to 2012 (N = 311*)

	Coronary Artery Aneurysms		
Variable	Negative (N = 257)	Positive (N = 54)	*P* Value†
Demographic characteristics			
Age <1 yr, n/N (%)	54/257 (21)	21/54 (39)	0.005
Gender, male, n/N (%)	158/256 (62)	43/54 (80)	0.012
Laboratory criteria			
Albumin, mean g/dL (SD)	3.7 (3.3)	4.3 (5.2)	0.524
GPT, mean U/L (SD)	68.6 (89.3)	72.5 (96.5)	0.780
C-reactive protein, mean mg/L (SD)	105.6 (82.4)	113.4 (92.2)	0.535
Leukocytosis at day 7, mean 1000/μL (SD)	14.8 (8.4)	14.9 (7.5)	0.974
Thrombocytosis at day 7, mean 1000/μL (SD)	537.0 (220.6)	503.4 (222.3)	0.326
Anemia for age, n/N (%)	161/257 (62.7)	36/54 (66.7)	0.577
Treatment			
Days after fever onset, mean (SD)	6.3 (2.8)	8.4 (6.5)	<0.001
Repeat IVIG dose, n/N (%)	58/239 (24)	19/48 (40)	0.029
High-dose aspirin, n/N (%)	222/250 (89)	46/51 (90)	0.771
Steroids, n/N (%)	25/253 (10)	9/52 (17)	0.121

*Coronary artery status was not reported in 4 cases.
†Pearson χ^2 for categorical variables and *t* test *P* value for continuous variables.
GPT indicates glutamate pyruvate transaminase; SD, standard deviation.

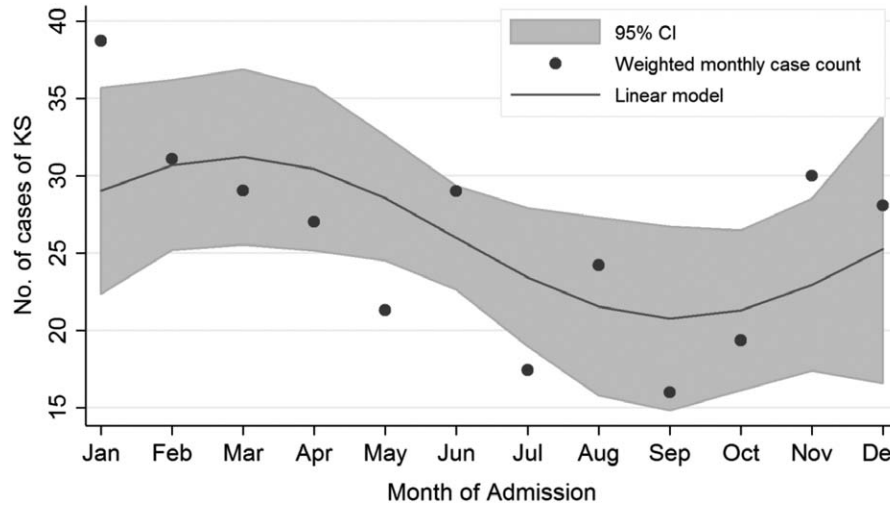

FIGURE 2. Seasonality of KD hospitalizations in children younger than 5 years in Germany from 2011 to 2012. Monthly case counts of KD hospitalizations in children younger than 5 years of age in Germany 2011 to 2012 weighted by the length of the month (No. of cases occurring in a month × 30/[No. days in the month]) and fitted to a sine curve. Peak-to-trough ratio was 1.6 (95% CI: 1.1–2.2), and the peak was on January 22.

of 6.4 of 100,000 (95% CI: 6.2–7.2). However, 2-source CRC suffers from a range of biases, including heterogeneity of capture probabilities and source dependence.[26] On stratification by age and gender (2 factors strongly associated with KD), the sum of the subgroup estimates was similar to the crude estimate. However, there was a substantial overlap between the data sets (>90% of ESPED cases "captured" by hospital surveillance), and therefore, likely dependence between the sources that cannot be statistically tested in a 2-source CRC.[32] To account for this, we also report Chao estimate[29] (7.2 of 100,000; 95% CI: 6.4–10.1), which is believed to be less biased than Chapman estimate when independence between sources is in doubt.[27] To validate our estimates, we reviewed the German national discharge records for discharge diagnosis of KD (ie, International Statistical Classification of Diseases and Related Health Problems 10th revision code M30.3). Multiple discharges may be attributed to a single case, and thus, it is unlikely that the incidence of hospital discharges would be less than the true incidence of cases (underreporting notwithstanding). Based on these records, the estimated annual KD incidence for the years 2011 and 2012 was 9.6 of 100.000, which is more consistent with the Chao estimate, being just within the upper bound confidence limit. While acknowledging the limitations of CRC, we consider Chao estimate to be a more reliable reflection of the "true" incidence. Our findings are broadly consistent with recent estimates from neighboring countries, such as those from the Netherlands, where underreporting was not accounted for.[10]

Historical estimates of KD incidence may be biased by the recent shift in KD case definitions (first published in 2004)[21], heightened physician awareness and improved diagnostics. Reports including incomplete cases may also have contributed to recent increases in estimated incidence rates.[12] Of 315 KD cases identified in this study, 20% were diagnosed as incomplete KD cases: 12% of those on the basis of positive echocardiography and an additional 8% on laboratory findings alone. This is consistent with other studies where both echocardiographic and laboratory findings have been reported.[10,12] In England, where KD incidence has been estimated repeatedly, incidence rates doubled[13] from 4.0 of 100,000 in 1991 to 8.4 of 100,000 in 2003.[14] However, the most recent estimate of 9.1 of 100,000 in 2012 (Gillian Hall, personal communication, May 2015) suggests that the incidence rates may have stabilized in recent years. Overall, incomplete cases were younger than complete cases, and two thirds of children diagnosed on the basis of laboratory criteria only were younger than 1 year . One third of incomplete cases were diagnosed using echocardiographic criteria, which supports the role of cardiac imaging in detecting cardiac complications and in securing the diagnosis of KD. Basic hematologic parameters (ie, thrombocytosis and leukocytosis) were also more commonly altered in younger children. In the absence of reliable diagnostics for KD, significant underdiagnosis or delayed diagnoses may occur resulting in an increased risk of CAAs, particularly in younger infants. Additional markers to distinguish KD from other clinical entities are the subject of ongoing research (eg, the analysis of specific urine proteomics[33]), but associations have not yet been confirmed. For this reason, such tests have not yet been implemented in routine clinical practice. In terms of treatment, our patient cohort clearly benefitted from early IVIG administration, and late administration was shown to be a risk factor for development of CAA. Other risk factors included young age and male gender.

Seasonal variation in Germany was confirmed, with a winter peak in KD hospitalizations. ESPED report rates by federal states were variable, and the SMR exceeded the national mean in 2 states, ie, Bavaria and Brandenburg. This may simply reflect regional report bias. No correlation was found between report rates and potential risk factors including population density, proportion of land under farming and proportion of high-risk ethnic groups at state level. However, formal testing for spatial-temporal clustering would be required to investigate these findings further.

There were some limitations to this study (in addition to CRC limitations discussed previously). To prevent overreporting of infants with fever of unknown origin who were also suspected to have KD, we only included children who were treated with IVIG. Therefore, some children with true KD—who were not treated with IVIG—will have been missed.

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