PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2016) **58**, 1140–1145 doi: 10.1111/ped.12970

Original Article

Temporal and geographical clustering of Kawasaki disease in Japan: 2007–2012

Takashi Sano, Nobuko Makino, Yasuko Aoyama, Ryusuke Ae, Takao Kojo, Kazuhiko Kotani, Yosikazu Nakamura and Hiroshi Yanagawa

Division of Public Health Center for Community Medicine Jichi Medical University, Shimotsuke, Tochigi, Japan

Abstract ***Background:*** Since 1987, no study has reported the municipal-level geographical clustering of Kawasaki disease (KD) in Japan. Therefore, the aim of the present study was to identify the temporal and municipal-level geographical clustering of KD.

Methods: The annual incidence rates of KD for each municipality were calculated using nationwide data from 73 758 patients with KD (2007–2012). To determine whether temporal and municipal-level clustering existed, we calculated the correlations of the annual incidence rates for each municipality during the study years, and compared these rates with those of the adjacent municipalities. Spatial scanning analysis was used to identify the geographical clusters for each year, and the incidence rates in those clusters were compared with the rates in the surrounding region.

Results: The annual national incidence rate of KD, adjusted for the prefecture-specific response rate, was 322.45 patients per 100 000 children aged 0–4 years. The correlation between the annual incidence rates during 2 consecutive years was significantly positive (coefficients, 0.149–0.428). On spatial scanning analysis, the most likely clusters were in the Tokyo metropolitan area during 2007–2010 and 2012, and in Kumamoto prefecture during 2011.

Conclusion: Kawasaki disease exhibits temporal and municipal-level clustering.

Key words epidemiology, incidence study, Japan, mucocutaneous lymph node syndrome, space–time clustering.

Kawasaki disease (KD) is a self-limiting vasculitis that frequently occurs in children aged <5 years old. Although approximately 50 years have passed since Dr. Kawasaki first reported this disease in 1967,[1] its etiology remains unknown. It is known, however, that the monthly incidence rate of KD in Japan is bimodal, with a high rate during winter and summer, and a low rate during autumn.[2] Furthermore, the annual incidence rate has increased gradually, with the exception of three significant outbreaks.[2] A previous study investigated the incidence rates in each Japanese municipality during 1977–1984, and reported that the annual municipality-specific incidence rates were significantly correlated between the study years.[3] Although subsequent studies have reported temporal clustering in prefecture units[4,5] or secondary medical care area units in Hokkaido and Shikoku,[6] no studies have performed a national municipality-specific investigation. Therefore, the present study was designed to calculate the annual municipality-specific KD incidence rates throughout Japan during 2007–2012, using data from the 20th, 21st, and 22nd nationwide KD surveys.[7–9] Based on these data, spatial scanning analysis was used to evaluate the existence of municipal-level and regional clustering during each study year. Furthermore, we calculated the monthly incidence rates in detected clusters, and compared them with the rates from the surrounding regions, in order to determine whether temporal clustering was present.

Correspondence: Takashi Sano, MD, Division of Public Health Center for Community Medicine Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan. Email: tkshsn34@jichi.ac.jp

Received 2 December 2015; revised 1 February 2016; accepted 29 February 2016.

Methods

The annual national KD incidence rates were calculated using data and address codes from 73 686 patient records obtained during the 20th, 21st, and 22nd nationwide KD surveys. We also calculated the municipality-specific number of cases (after adjusting for the prefecture-based response rates), and calculated the annual municipal incidence rates per 100 000 children aged 0–4 years. The municipal regions were identified using the boundaries that were in place on 1 January 2013, and the populations of 0–4-year-old children were calculated using the 2010 national census data (Fig. 1).

We extracted municipalities that had a sufficiently large population to ensure a 0.95 probability of returning at least one case during each year, based on the assumption of a Poisson distribution and the 6 year average national KD incidence rate. Next, we calculated the year-to-year correlations between the municipality-specific incidence rates during all 6 study years. We then categorized the municipalities into quintiles using average annual incidence rates, and scored each municipality according to the annual incidence rate (i.e. each municipality was assigned a score of 1–5 for each study year, based on that year's incidence rate). To identify municipalities that had a high or low incidence rate trend during the 6 years, we defined low incidence rate trend as a municipality 6 year cumulative score of 6–10, and a high incidence rate as a 6 year cumulative score 26–30. Chi-squared test was used

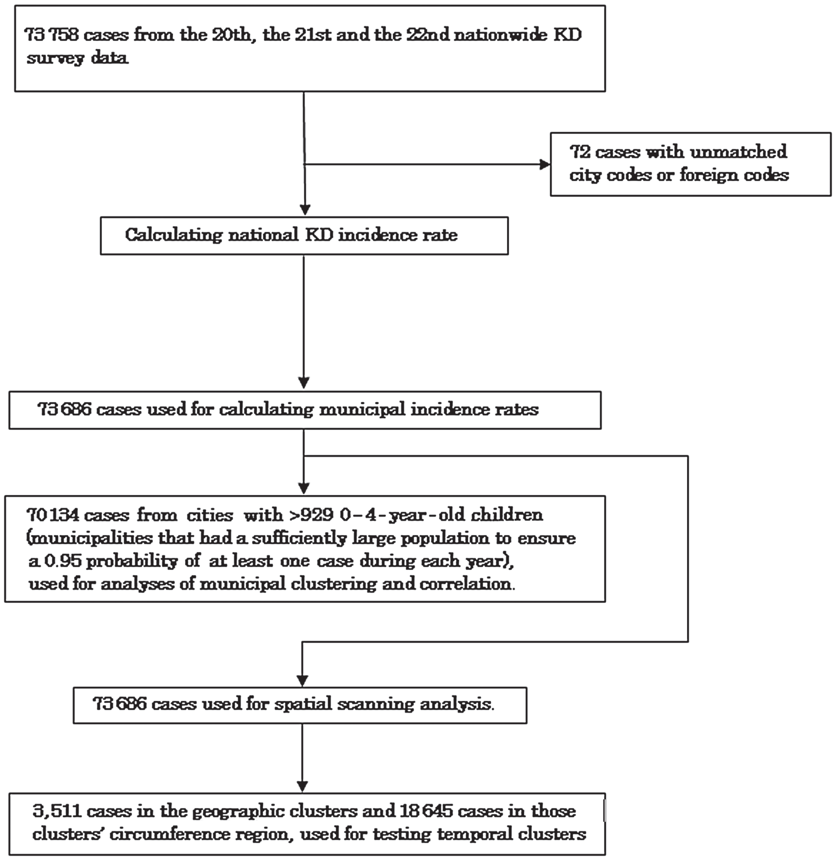

Fig. 1 Study flowchart. KD, Kawasaki disease.

to compare cumulative score with expected score, calculated based on the assumption that the municipal incidence rates were completely random.

Next, we identified all pairs of adjacent municipalities using the Japanese Geospatial Information Authority data,[10] and extracted municipality pairs for which both municipalities were predicted to return at least one case of KD. These pairs were then numbered using each municipality's annual quintile score (i.e. 1–1, 1–2, 1–3… 4–5, and 5–5) in order to grade each pair. To determine whether the KD incidence rates in the two adjacent municipalities tended to be similar or dissimilar, we used the chi-squared test to compare the pairs having identical scores (i.e. 1–1, 2–2, 3–3, 4–4, and 5–5) and pairs having different scores (i.e. 1–2, 2–3…3–4, and 4–5) with their expected distributions.

We defined the presence of municipal KD clustering based on a significant correlation within the annual municipal KD incidence rates. Geographical clustering was defined as similar annual KD incidence rates for two adjacent municipalities, and we examined these clusters during each study year using the Kulldorff method of spatial scanning analysis.[11] This method can identify the most likely geographical clustering based on the municipalities' populations, number of disease cases, and geographical data. If geographical clusters were observed, we compared the monthly incidence rates in the cluster regions and their surrounding regions. Furthermore, we evaluated the correlations between the municipal populations of children aged 0–4 years and the annual KD incidence rates, in order to determine whether the population size affected KD incidence rate.

Statistical analysis

Statistical analysis was done using the chi-squared test in SPSS version 23 (SPSS, Chicago, IL, USA) and Kulldorff analysis in R version 3.2.0 (R foundation, Vienna, Austria).

Results

Between 2007 and 2012, 73 758 patients with KD were registered in the Japanese survey database. After adjusting for the prefecture-specific response rates, we calculated the total number of patients with KD as 102 476, and the 2010 census data indicated that the total population of 0–4-year-old Japanese children was 5 296 748. Therefore, the annual national KD incidence rate was calculated to be 322.45 patients per 100 000 children aged 0–4 years. When we compared the prefecture-specific response rates and the response-adjusted incidence rates, the correlation coefficient was 0.042 (P = n.s.). Based on the national incidence rate, we determined that municipalities required a population of >929 children aged 0–4 years to provide a 0.95 probability of returning at least one case per year. Among the 1740 Japanese municipalities, 868 municipalities (50.8%) fulfilled this criterion, and we analyzed 70 134 cases (95.1%) from these municipalities (Fig. 1).

Table 1 lists the distribution of the 868 municipalities' annual incidence rates. During the study period, the distribution gradually shifted towards higher incidence rates. Furthermore, some areas had an accumulation of municipalities with high incidence rates throughout the study period (Fig. 2). Table 2 lists the year-to-year correlation coefficients for the 6 study years and 868 municipalities; all correlations were significant ($P < 0.01$).

Table 1 Distribution of annual municipal incidence rates†

Incidence rate (per 10 000 aged 0–4 years per year)	Calendar year						
	2007	2008	2009	2010	2011	2012	All
0–99	133	126	125	116	102	81	34
100–199	148	146	152	136	130	108	112
200–299	193	194	198	155	163	148	249
300–399	194	207	206	179	192	180	289
400–499	108	106	105	139	144	172	152
500–599	47	60	37	90	71	97	27
600–	45	29	45	53	66	82	5
Total	868	868	868	868	868	868	868

†All municipal populations >929 children aged 0–4 years.

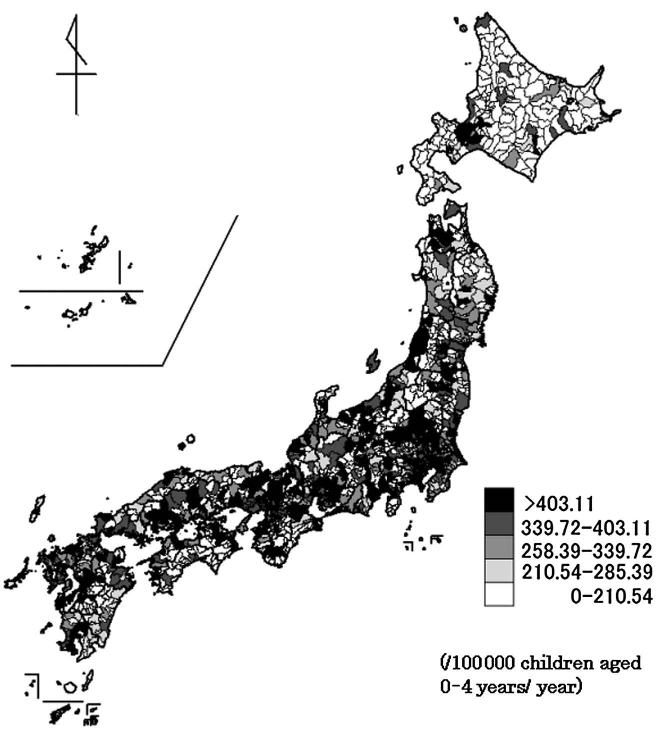

Fig. 2 Average 6 year municipality annual incidence rate of Kawasaki disease.

Table 2 Correlation coefficients of annual municipal incidence rates

	2007	2008	2009	2010	2011
2008	0.428**				
2009	0.294**	0.278**			
2010	0.184**	0.196**	0.355**		
2011	0.178**	0.157**	0.226**	0.272**	
2012	0.162**	0.149**	0.255**	0.242**	0.394**

$^{**}P < 0.01$ (two-tailed).

Table 3 lists the distributions of each municipality's 6 year cumulative incidence rate score. There were significant differences in the distributions of municipalities with relatively high scores (score, 26–30) or relatively low scores (score, 6–10), compared with the expected distributions (both, $P < 0.001$, χ^2 test). Thus, we confirmed that municipal-level clustering of KD was present during the study period. Table 3 also lists the results of analysis of municipalities with the same or difference score: there was a significantly greater distribution of pairs with the same scores (vs the expected random distribution), confirming that the geographical clusters consisted of more than one municipality.

Figure 3 shows the most likely geographical clusters for 2007–2012, identified using the Kulldorff method. The metropolitan Tokyo area had the most likely geographical clusters during 2007–2010 and 2012 (the second most likely areas were as follows: Sapporo City during 2007, 2009 and 2010, Keihanshin area during 2008, and Nagoya City during 2012), and Kumamoto prefecture had a geographical cluster during 2011 (the second most likely area was the Gunma prefecture). Figure 4 shows the monthly incidence rates in each geographical cluster for each year, and in the specific regions within each cluster. Because monthly incidences are small numbers, we did not adjust them with the prefecture-specific response rates. The confidence interval for each monthly incidence rate was calculated using the population of 0–4-year-old children, based on the assumption of a Poisson distribution. The monthly incidence rate patterns in the metropolitan Tokyo clusters were similar to those in the Kanto region, although the Kumamoto cluster had a different pattern from that in the Kyushu region. The Kumamoto cluster's monthly incidence rates during May, June, and December were all significantly higher than those in the Kyushu region (May: OR, 1.97, 95%CI: 1.28–3.00; June: OR, 1.97, 95%CI: 1.30–3.00; December: OR, 2.30, 95%CI: 1.55–3.42).

Table 4 lists the correlations between the municipal populations of 0–4-year-old children and the annual or 6 year KD incidence rates. The 6 year KD incidence rate was significantly correlated with the municipal population of 0–4-year-old children (correlation coefficient, 0.799; $P < 0.01$).

Discussion

The present finding of municipal-level clustering of KD confirms the findings of a previous study,[3] which reported that there was municipal-level clustering and a positive correlation between the population of children and the incidence rates of KD. The prefecture-specific response rates were not strongly correlated with the adjusted incidence rates. If hospitals with many patients tend to have a higher or lower response rate than hospitals with only a few patients, some correlations could be found. Therefore, it appears that there were no evident unnecessary adjustments.

Interestingly, the existence of annual municipal-level clusters indicates that there are some region-specific factors that are related to the etiology of KD. One possible factor is a large population of

Table 3 Six year incidence rate trends: Observed vs expected

		Observed	Expected	Observed/Expected
6 year trend of incidence rates (total quintile number)	Lowest (6–10)	80	11.67	6.86
	Lower (1–15)	195	196.38	0.99
	Middle (16–20)	298	451.92	0.66
	Higher (21–25)	232	196.38	1.18
	Highest (26–30)	63	11.67	5.40
Combination of adjacent municipalities' quintile number	Same (1–1,… 5–5)	897	677	1.32
	Different (1–2, … 4–5)	2488	2708	0.92
	Sum	3385	3385	1

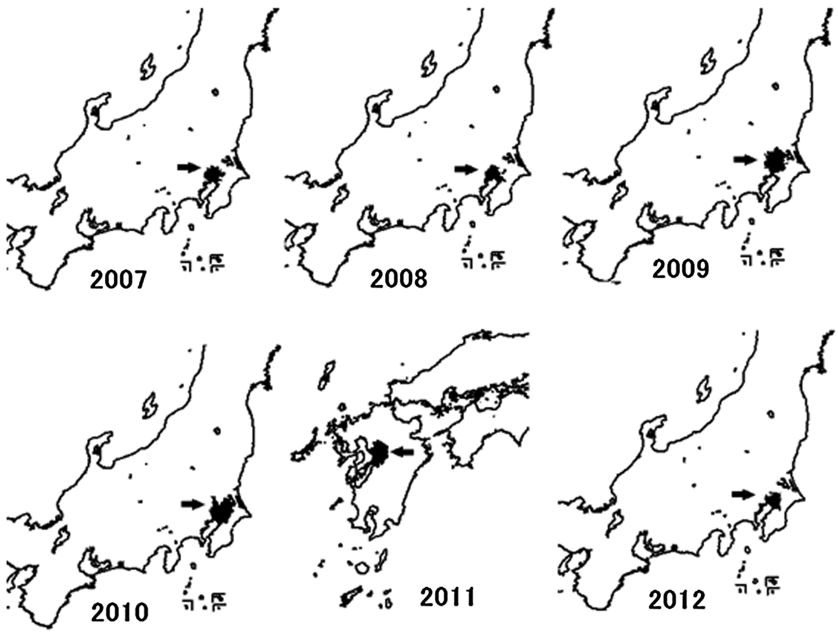

Fig. 3 Most likely geographic clusters (arrow) on Kulldorff spatial scanning test ($P < 0.001$). Maps drawn using MANDARA version 9.4.1 (Kenji Tani, Saitama University, Saitama, Japan).

children, given that the metropolitan Tokyo area has the largest population of children in Japan, and this area contained clear geographical clusters during several study years. The overall incidence number in the metropolitan Tokyo clusters during those 5 years was 3293 (after adjustment, the incidence number was 4917.9) and the 5 year population in those clusters was 1 167 117 children-year. Therefore, the average incidence rate was 421.4 per 100 000 children aged 0–4 years, and it was 1.3-fold as high as the annual national rate (322.4). This large population hypothesis is also confirmed by the fact that the second most likely clusters were in large cities such as Sapporo City, the Keihanshin area and Nagoya city during 2007–2010 and 2012. Except for the Tohoku area, the municipal population size did not change so much in the study period. Therefore, municipalities with a small population may have had a low KD incidence rate during this period, and vice versa. Inter-person transmission may also be a factor, which would imply some form of person-to-person or person-to-environment-to-person route for infection with the pathogens that cause KD. Inter-person transmission factor can explain the similar incidence rate scores of the adjacent municipalities. Kumamoto (and Gunma), however, were sites of geographical clusters during 2011, indicating that there is likely some non-population-specific factor that influences outbreaks of KD, given that this region has a smaller population than many other Japanese cities.

During May–August 2011, Japan had a large outbreak of hand-foot-mouth disease (HFMD) and a small outbreak of herpangina,[12] mainly caused by Coxsackie virus A6.[13] The Kumamoto prefecture contained an abnormally large number of clinically confirmed HFMD cases,[12] and Coxsackie virus A16, Coxsackie virus A6, and Enterovirus 71 (EV71) were detected in patients with HFMD.[14] During the HFMD outbreak, EV71 was detected only in the Kumamoto prefecture,[12] indicating that it was also involved in the KD cluster in Kumamoto during 2011. There was also, however, a small outbreak of HFMD during 2010 that was mainly caused by EV71, although there was no increase in the number of KD cases during that outbreak. Therefore, it is unlikely that infection with EV71 can explain the KD cluster in Kumamoto prefecture during 2011.

Another possible explanation is that some HFMD or herpangina cases were misdiagnosed as KD. Among the 53 KD cases in Kumamoto during May–June 2011, 20 cases were identified as incomplete KD (≤five of six possible symptoms of KD). This prevalence of incomplete KD (37.7%) was twofold higher

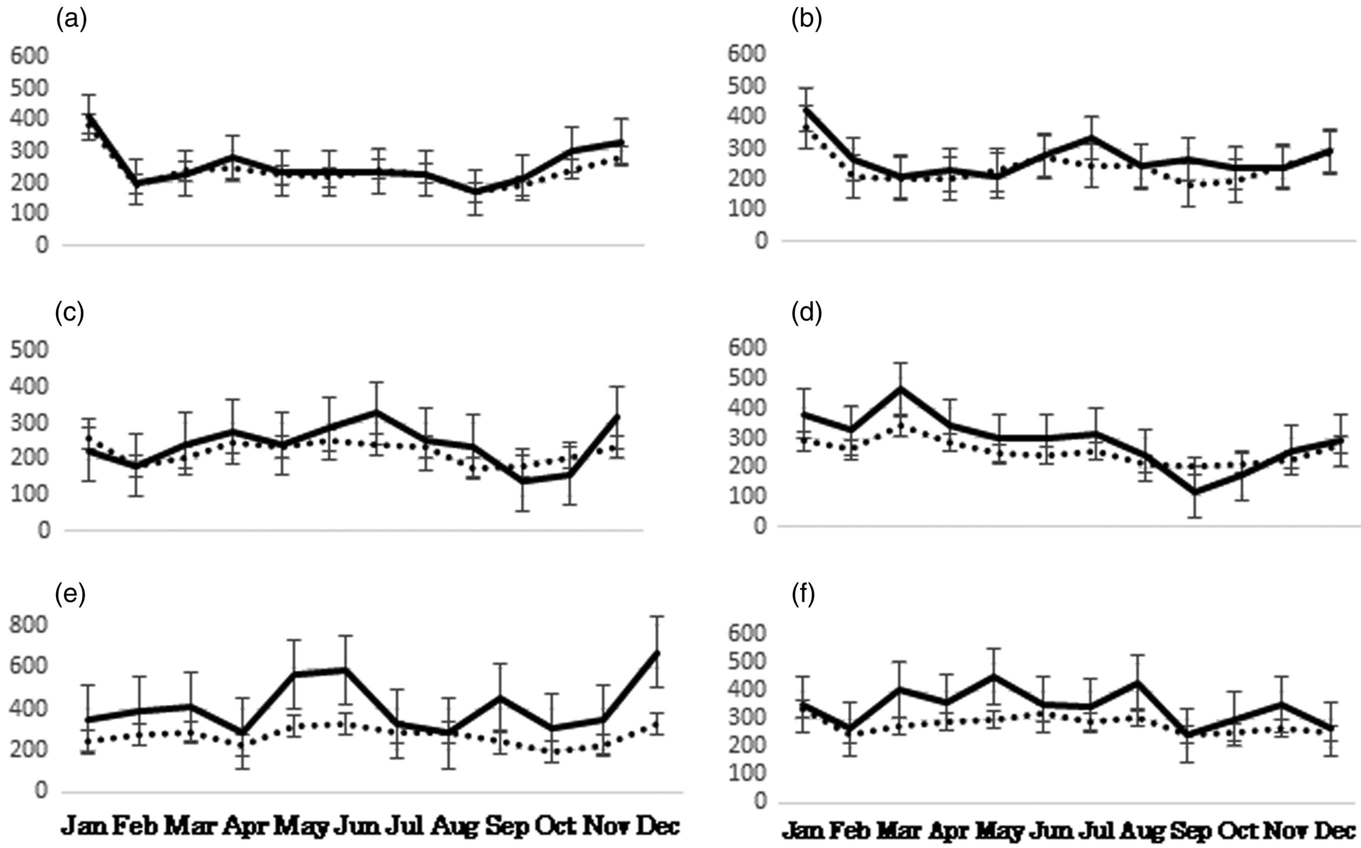

Fig. 4 Monthly incidence rates (per 100 000 aged 0–4 years/year) of the most likely cluster and region for (a) 2007; (b) 2008; (c) 2009; (d) 2010; (e) 2011; (f) 2012. (a–d,f) (····) Kanto; (—) cluster; (e) (····) Kyushu; (—) cluster.

Table 4 Annual municipality incidence rate

Population of children aged 0–4	No. observed municipalities	Yearly incidence rate (per 100 000 children aged 0–4 years) Calendar years						
		2007	2008	2009	2010	2011	2012	6 years
0–124	185	236.55	343.51	184.04	246.07	146.05	298.64	242.48
125–249	184	289.19	298.32	245.17	253.74	332.99	299.73	286.53
250–399	176	229.79	238.56	296.74	302.31	263.45	271.15	267.00
400–599	137	295.69	295.21	248.53	275.50	321.85	266.67	283.91
600–999	208	241.10	279.68	248.39	237.39	274.08	316.52	266.19
1000–1499	169	293.24	279.49	289.40	294.72	287.25	331.63	295.95
1500–1999	110	265.33	250.63	300.22	317.27	323.73	324.97	297.03
2000–3999	257	282.75	283.28	272.01	304.14	328.28	356.93	304.57
4000–6999	148	288.61	310.64	284.20	326.47	321.59	343.69	312.53
>6999	156	307.00	312.21	297.13	360.79	362.84	388.32	338.05
	r	0.531	0.277	0.424	0.775**	0.499	0.793**	0.799**

**$P < 0.01$ (two-tailed).

compared with the 6 year national average rate (18.7%) and that of the Tokyo metropolitan clusters during the other years (17.9%). Of these 20 incomplete KD cases, however, 16 cases involved four symptoms, and it is unlikely that HFMD or herpangina could explain four symptoms of KD. Furthermore, even if HFMD were misdiagnosed as KD in Kumamoto, this misdiagnosis would likely have occurred throughout the Kyushu region. The number of HFMD cases in Saga and Fukuoka prefectures in the Kyushu region, however, was higher than in Kumamoto prefecture,[12] implying that these prefectures should have had a corresponding increase in the number of KD cases. Furthermore, we compared the hospital ID distributions during May–June 2011 with the other months in the Kumamoto cluster, although we did not observe any significant differences. Thus, the approximately twofold greater monthly KD incidence rates in the Kumamoto cluster, compared with the Kyushu region, cannot be explained by misdiagnosis.

Environmental factors might also explain the Kumamoto cluster, because there were several small eruptions at Mount Aso (a volcano in Kumamoto) during May–June 2011. There were no increases, however, in the density of sulfur dioxide or of suspended particulate matter during these months, indicating that the eruptions likely did not affect the environment. Rodo *et al.* have also hypothesized that winds from northeastern China carried pathogens to Japan,[15,16] and Kumamoto had Asian dust storms from northeastern China during 1–13 May 2011. These dust storms, however, would also have affected the entire Kyushu region during that time, suggesting that these storms cannot explain the geographical cluster in Kumamoto.

With regard to Gunma prefecture, the incidence rates during May and July were significantly higher than monthly average of the Kanto region: 1.88-fold higher during May and 1.60-fold higher during July ($P < 0.05$). These high incidence rate periods occurred at almost the same time as those in Kumamoto, but Gunma prefecture was not affected by the aforementioned three factors (HFMD, volcanic eruption or Asian dust storm) during those months.

This study has several important limitations. First, although we adjusted the numbers of patients based on prefecture-specific response rate, we cannot exclude the possibility of bias at the level of the participating hospitals. Second, the populations of children were calculated based on the 2010 census data, but Japan experienced a large earthquake during 2011, and the estimated population of east Tohoku might be higher than the actual population (due to earthquake-related fatalities), especially in the Miyagi and Fukushima prefectures.

In conclusion, KD exhibits geographical and temporal clustering. The large population of children in metropolitan Tokyo during 2007–2010 and 2012 may explain the corresponding clusters observed, although unknown region-specific factors are likely responsible for the temporal clusters observed in Kumamoto prefecture during May, June, and December 2011 and in Gunma prefecture during May and July 2011. A non-population-specific and region-specific KD etiological study needs to be carried out in such clusters.

Disclosure

The authors declare no conflict of interest.

References

1 Kawasaki T, Kosaki F. Acute febrile muco-cutaneous lymph node syndrome in young children with unique digital desquamation (clinical observation of 50 cases observed at our institution). *Arerugi (Jpn. J. Allergol.)* 1967; **16**: 178–222.
2 Nakamura Y, Yashiro M, Uehara R. Epidemiologic features of Kawasaki disease in Japan: From the view point of the nationwide surveys. Pediatr. Cardiol. 2012; **28**: 148–56.
3 Nakamura Y, Yanagawa H, Kawasaki T. Temporal and geographical clustering of Kawasaki disease in Japan. Prog. Clin. Biol. Res. 1987; **250**: 19–32.
4 Yashiro M, Ojima T, Tanihara S *et al.* An analysis on time–space clustering of Kawasaki disease in recent 10 years in Japan. *J. Pediatr. Pract.* 1999; **3**: 419–25.
5 Burns JC, Cayan DR, Tong G *et al*. Seasonality and temporal clustering of Kawasaki syndrome. Epidemiology 2005; **16**: 220–25.
6 Yashiro M, Nakamura Y, Ojima T, Tanihara S, Oki I, Yanagawa H. Ten year observation of time–space relationship on incidences of Kawasaki disease in Japan, Analyses in Hokkaido and Shikoku. *J. Jpn. Pediatr. Soc.* 1999; **103**: 832–7.
7 Makino N, Nakamura Y, Yashiro M *et al*. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: From the results of the 22nd nationwide survey. J. Epidemiol. 2015; **25**: 239–45.
8 Nakamura Y, Yashiro M, Uehara R *et al.* Epidemiologic features of Kawasaki disease in Japan: Results of the 2009–2010 nationwide survey. *J. Epidemiol.* 2012; **22**: 216–21.
9 Nakamura Y, Yashiro M, Uehara R *et al.* Epidemiologic features of Kawasaki disease in Japan: Results of the 2007-2008 nationwide survey. *J. Epidemiol.* 2010; **20**: 302–7.
10 Geospatial Information Authority of Japan. Basic map information data download site. 2015. [Cited 1 August 2015]. Available from URL: http://fgd.gsi.go.jp/download/ (in Japanese)
11 Kulldorff M. A spatial scan statistic. *Commun. Stat. Theory Methods* 1997; **26**: 1481–96.
12 Infectious Disease Surveillance Center. [27th weekly report in 2011.] National Institution of Infectious Disease, Tokyo, Japan, 2011 (in Japanese).
13 Fujimoto T, Iizuka S, Enomoto M, Abe K, Yamashita K, Hanaoka N. Hand, foot, and mouth disease caused by coxsackievirus A6, Japan, 2011. *Emerg. Infect. Dis.* 2012; **18**: 337–9.
14 Prevalence of Enterovirus (EV) infection and genetic analysis of EV detected from the aseptic meningitis patients in Kumamoto prefecture. Health Environmental Science Research Institute of Kumamoto prefecture, Udo city, Kumamoto prefecture, 2012 (in Japanese).
15 Rodo X, Ballester J, Cayan D *et al*. Association of Kawasaki disease with tropospheric wind patterns. Sci. Rep. 2011; **1**: 1–7.
16 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. *Proc. Natl Acad. Sci. USA* 2014; **111**: 7952–7.