



Association of kawasaki disease with tropospheric wind patterns

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The causal agent of Kawasaki disease (KD) remains unknown after more than 40 years of intensive research. The number of cases continues to rise in many parts of the world and KD is the most common cause of acquired heart disease in childhood in developed countries. Analyses of the three major KD epidemics in Japan, major non-epidemic interannual fluctuations of KD cases in Japan and San Diego, and the seasonal variation of KD in Japan, Hawaii, and San Diego, reveals a consistent pattern wherein KD cases are often linked to large-scale wind currents originating in central Asia and traversing the north Pacific. Results suggest that the environmental trigger for KD could be wind-borne. Efforts to isolate the causative agent of KD should focus on the microbiology of aerosols.

Kawasaki disease (KD) is a pediatric self-limited vasculitis that is the most common cause of acquired heart disease in children in the US and Japan^{1,2}. KD is characterized by immune-mediated damage to the coronary arterial wall and myocardium. Approximately one-quarter of untreated patients will develop coronary artery aneurysms, which in some cases can lead to myocardial infarction and death³⁻⁵. As there is no diagnostic test, confirmation of cases relies solely on the identification of a constellation of clinical signs that include fever, rash, conjunctival injection, cervical lymphadenopathy, changes in the oral mucosa, and edema and erythema of the hands and feet in association with laboratory studies showing marked systemic inflammation^{3,6-7}. Although Kawasaki saw his first patient in 1960 and in the ensuing 50 years many etiologies have been proposed^{8,9}, the agent that triggers the inflammatory response has still not been identified¹⁰. Although temporal and spatial clustering of cases has been reported, nothing is known about the factors that influence KD seasonality^{11,12}. Increasing KD incidence has been documented in many regions with Japan as the most dramatic example^{13,14}. However, whether this represents improved case recognition or an actual increase in KD incidence remains a matter of ongoing debate. The seasonality of KD has been noted in many regions but has been most extensively studied in Japan, the country of highest incidence, where the cause for the seasonal variation of cases still remains a mystery^{11,15-19}.

In the present study, an analysis of time series of KD patients in three geographically distant regions suggests that the agent responsible for KD is transported through broad scale wind currents. Using a set of analyses that separately considers the 3 major epidemics in Japan, the recurrent seasonal cycle at each of the three locations, and the interannual, year-to-year variability in Japan and San Diego, we show how fluctuations in numbers of KD cases are associated with similar fluctuations in the wind circulation. The seasonal analyses suggest that the peak in KD cases at each of the three locations is linked to a coherent seasonal shift in winds that simultaneously exposes Japan to air masses from central Asia, and Hawaii and California to air masses from the western North Pacific. The interannual analysis also suggests that the enhancement of this trans-Pacific circulation pattern is associated with unusually high KD activity in Japan and San Diego.

Results

Epidemics. The monthly time series for KD cases in Japan since 1970 showed two dramatic nationwide epidemics lasting several months and peaking in May 1982 (16,100 annual cases) and March 1986 (14,700 annual cases), respectively. A third epidemic, much lower in magnitude, peaked around April 1979 (6,700 cases) (Figure 1a). These three peaks represent the largest KD epidemics events ever recorded worldwide and provide an opportunity

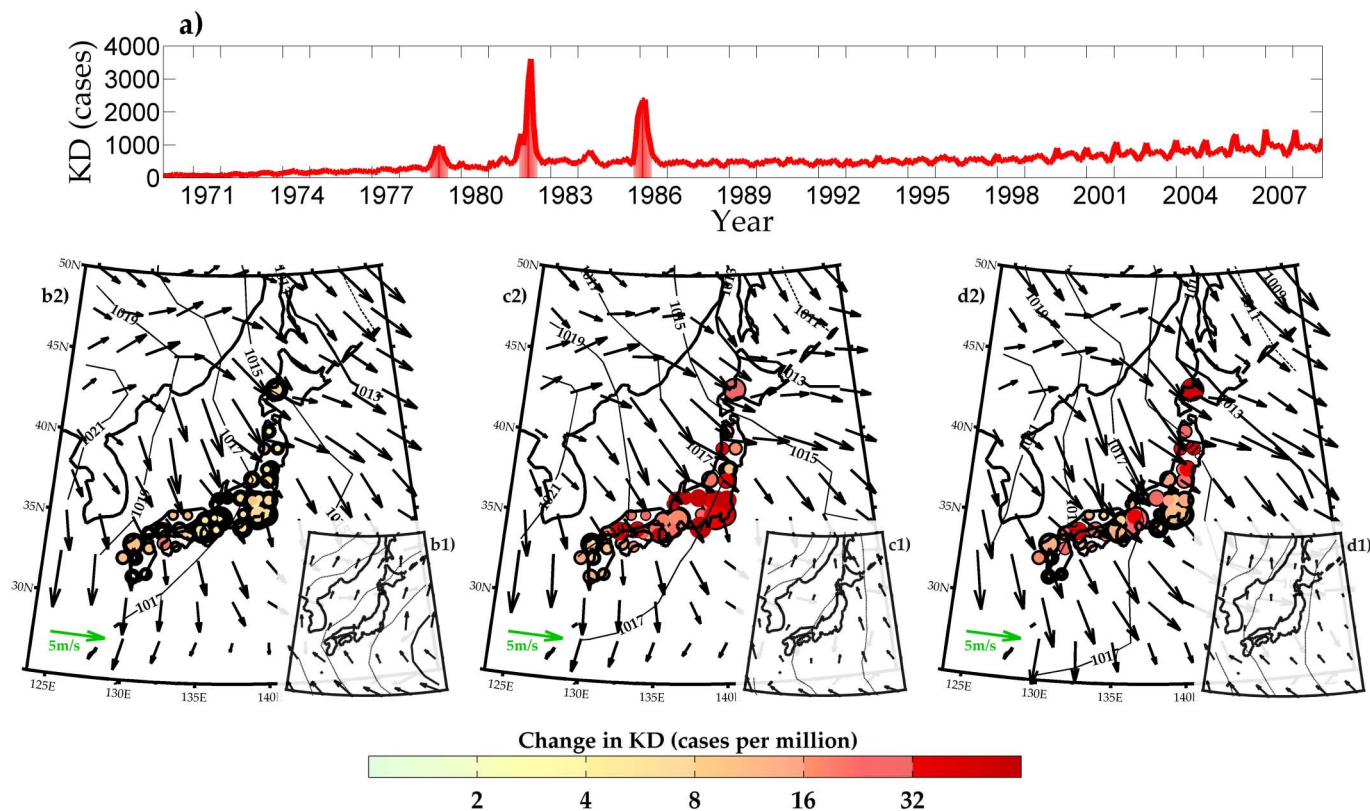


Figure 1 | Major epidemics of monthly KD incidence in Japan. The three main historical KD epidemics are highlighted in red in panel a (cases). Time averaged sea level pressure (hPa) and surface winds (m/s) prior to the March/May 1979, May 1982 and March 1986 epidemics are shown in panels b, c and d, respectively. Monthly atmospheric variables were averaged for the preceding summer (JJA 1978 in b1, JJA 1981 in c1, and JJA 1985 in d1), when winds from the south typically blow across Japan, and for the rising phase of the epidemics, from September to the last month before the peak (Sep 1978 to Mar 1979 in b2, Sep 1981 to Apr 1982 in c2, and Sep 1985 to Feb 1986 in d2), when winds shifted and blew from the northwest. Colored dots depict the increase in KD incidence (per million inhabitants) by prefecture between the preceding September and the peak (Apr 1979 minus Sep 1978 in b2, May 1982 minus Sep 1981 in c2, and Mar 1986 minus Sep 1985 in d2).

to investigate KD dynamics and possible climate relationships. To investigate a possible influence from large scale environmental factors, sea level pressure and surface winds were averaged for the June–July–August summer months before the onset of the epidemics (panels b1, c1 and d1 in Figure 1), and from September to the month prior to the peak in KD cases (panels b2, c2 and d2).

Prior to the beginning of the epidemic peaks, low numbers of KD cases coincided with southerly winds (winds from the south) blowing over Japan for the entire summer (panels b1, c1 and d1 in Fig.1), a wind pattern which corresponds to the typical summer climatological configuration (e.g. see Supplementary Video 1). Immediately after the beginning of autumn, the number of cases rapidly mounted all over Japan when winds turned northwest in direction. Colored dots in panels b2, c2 and d2 illustrate the synchronization of the increase in KD cases throughout Japan coinciding with a shift to northwesterly winds in both peaks. Just after the peak in each epidemic, the winds again shifted and blew from the south, and a marked decrease in the number of KD cases occurred (*results not shown*).

Interannual anomalies. To investigate further whether the influx of air from continental Asia is associated with fluctuations in numbers of KD cases, the Japanese dataset spanning the period from 1987–2006 was examined (Supplementary Figure 1). This segment of the time series excluded the major KD epidemics in Japan discussed above. Therefore, major interannual peaks and troughs of KD cases in Japan were selected for this post-epidemic period (red and blue anomalies in Figure 2a, respectively), and corresponding atmospheric anomalies were then composited. Years with increased

numbers of KD cases in Japan were significantly associated with enhanced local northwesterly winds, as a result of an anomalous area of low pressure centered to the north of Japan (Figure 2b). Conversely, the composite of the major troughs in KD cases was linked to a quite different pattern in which an area of anomalous high pressure developed over the border between Russia and China, thus driving northeasterly winds from the Pacific Ocean across Japan (Figure 2c).

To assess whether year-to-year variations in wind patterns are associated with interannual fluctuations in KD numbers on the other side of the North Pacific, similar analyses were conducted for San Diego. The atmospheric connection from continental Asia to Japan and San Diego is complex, and the atmospheric pathways connecting both shores of the Pacific can result from many different trajectories throughout the North Pacific. However, it was possible from this analysis to allocate all major interannual peaks of KD cases occurring in San Diego during the 1994–2008 period as belonging to two main atmospheric configurations. On the one hand (during green peaks in Figure 3a: 1994/95, 1997/98, 2002/03, 2004/05), zonal winds were intensified in the subtropics between 25N and 35N (Figure 3b and Supplementary Figure 2a), thus connecting the Asian continent and Japan to San Diego along a direct zonal path developing at all vertical levels (Figure 3c and Supplementary Figure 2c). On the other hand (during orange peaks in Figure 3a: 1999, 2006, 2007/08), the zonal trajectory appeared to be blocked in the subtropics (Figure 3d and Supplementary Figure 2b), but an alternative and shorter (in terms of distance) geodesic path was opened across the northern extratropics (Figure 3e and Supplementary Figure 2d), with enhanced westerly winds developing there. Therefore, interannual wind anomalies were

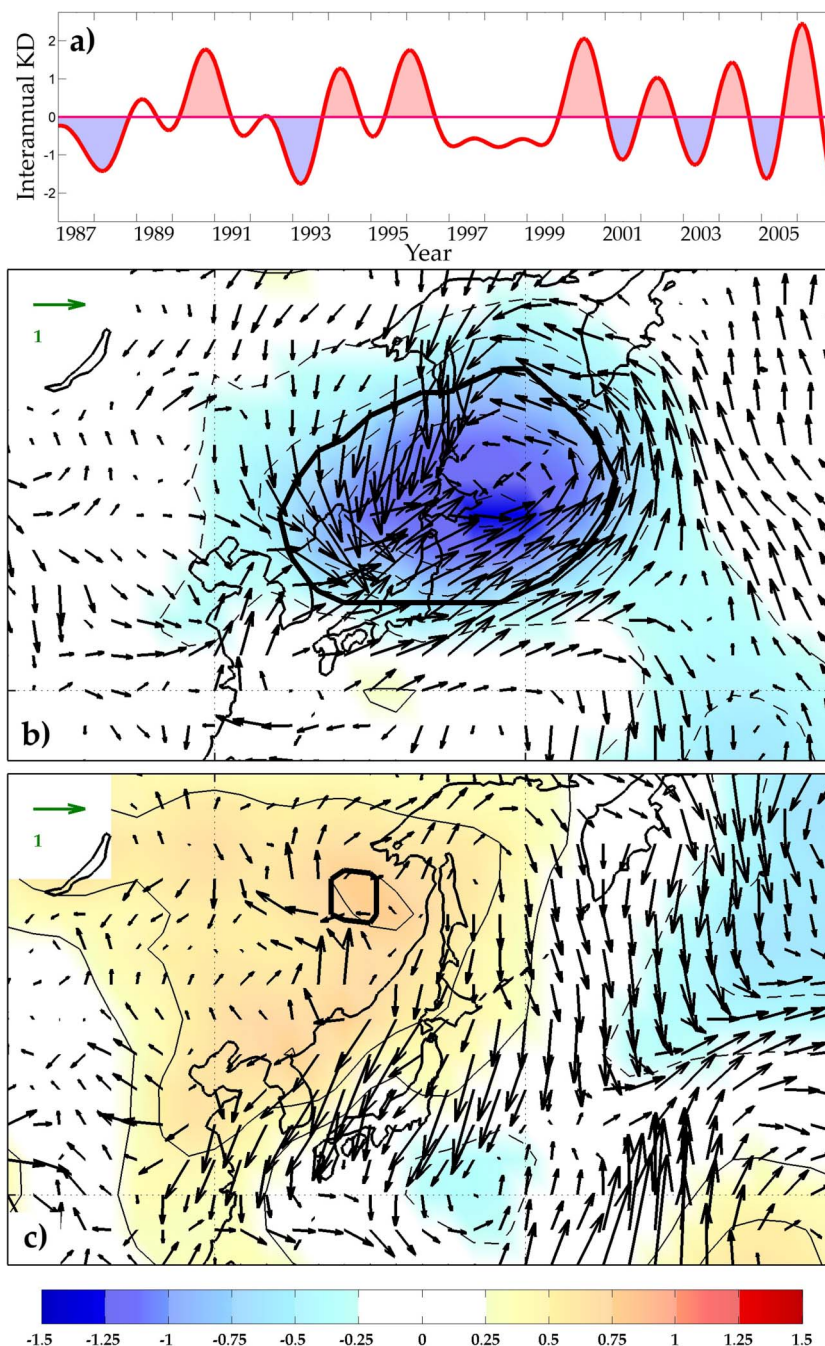


Figure 2 | Surface configuration for the major interannual peaks of KD incidence in Japan. Panel a depicts the standardized (unitless) interannual reconstructed component of the original monthly time series of KD shown in Supplementary Figures 1a. The 7 (5) interannual peaks (troughs) reaching the +1 (−1) standard deviation criterion are dashed in red (blue). Standardized (unitless) interannual anomalies of sea level pressure and surface winds were composited in panel b (c) for the set of months when these peaks (troughs) were observed. Thick contours depict regions with significant interannual sea level pressure anomalies ($p < 0.05$).

associated with peaks in the numbers of annual KD cases in San Diego with the trajectory operating at different latitudes in two main patterns. Similar analyses were performed for other meteorological variables exhibiting seasonality, including minimum and maximum temperature, soil moisture and precipitation, but a similar association with KD did not emerge (*results not shown*).

Seasonal cycle. Seasonality represents a prominent contribution to the overall variance in the number of KD cases in Japan, especially when compared to interannual variability of the disease (44% vs. 11%, respectively). Examination of KD time series from Japan, San Diego and Hawaii show a nearly synchronized peak in KD activity

from November through March (cf. Figures 4a–c), suggesting a shared mechanism explaining the seasonality of the disease in the three sites. A comparison between the number of KD cases and wind patterns was performed for the interval 1996–2006, the period for which there was data for all three study sites (Figure 4 and Supplementary Figure 3). In Japan, northwesterly winds (NW-WIND) were studied by projecting the observed winds onto a unit vector in the northwest/southeast direction in order to conform to the results observed in Figures 1b2,c2,d2 and 2b. Thus, positive values of NW-WIND correspond to winds blowing from the north, northwest or west, while negative values correspond to winds from the south, southeast or east. To characterize the

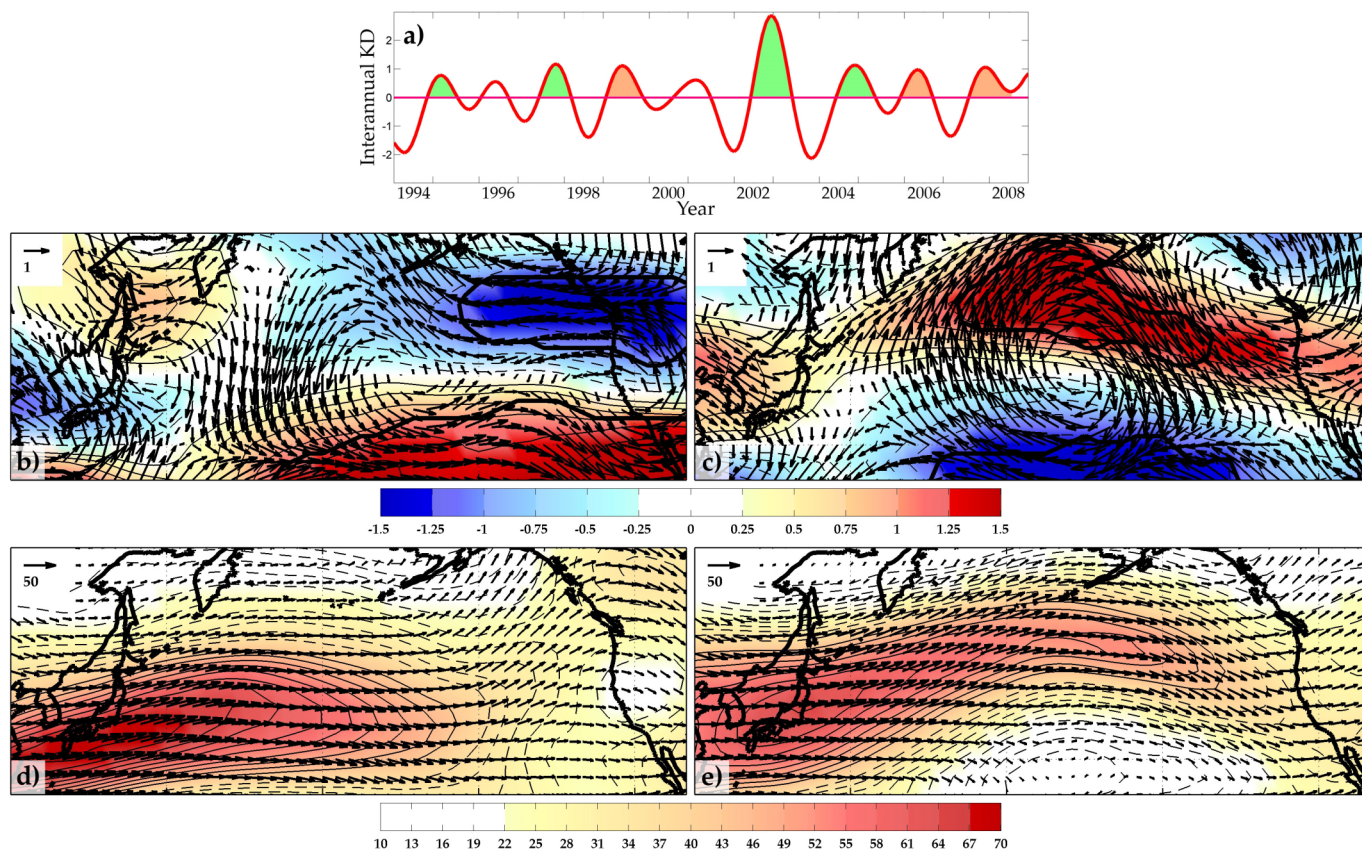


Figure 3 | Upper-troposphere wind configuration for the major interannual peaks of KD incidence in San Diego. Panel a depicts the standardized (unitless) interannual reconstructed component of the original monthly time series of KD shown in Supplementary Figures 1c. Standardized (unitless) interannual anomalies (b,c) and actual observations (d,e) of 300 hPa wind direction and intensity were composited for the 4 green (b,d) and 3 orange (c,e) interannual peaks in panel a. Thick contours in panels b and c depict regions with significant interannual wind intensity anomalies ($p < 0.05$).

pathway across the north Pacific from continental Asia and Japan to Hawaii and San Diego (e.g. Figures 3b–e), a Pacific Zonal Wind Index (P-WIND) was defined as the mean of the zonal component of winds along the subtropical north Pacific (see the horizontal green line in Figures 5a,b).

The coherence between NW-WIND, wind intensity (WI) and KD cases in Japan mirrored the relationship found for the main KD epidemics and the interannual anomalies (Figure 4a and Supplementary Figure 3a). The number of KD cases was indeed highest in winter, when strong northwesterly winds blow across Japan from central Asia. In contrast, there are fewer KD cases during the rest of the year, when winds become weaker or even change direction. Farther east, a similar coherence between the number of KD cases in San Diego and Hawaii and P-WIND was observed (Figures 4b,c and Supplementary Figure 3b,c). Minor peaks in other seasons were also evident. The Empirical Orthogonal Function (EOF) decomposition, applied to both KD and winds, recovered all main sub-annual variability portions in the two variables. Both contained a summer peak, wherein there is a return to northwesterly wind currents, consistent with the association to the major KD peak in cases in winter (Supplementary Figure 4).

The seasonal structure of NW-WIND is very similar to that of P-WIND, as both share the same driving atmospheric configuration emerging in winter in the North Pacific (Figure 5 and Supplementary Videos 1–3). In the lower troposphere, the high and low pressure areas near Siberia and the Aleutian Islands, respectively, reach the highest intensity in December and January, when they cover the whole eastern Asian continent as well as the extratropical North Pacific. During the entire winter, but especially in these months,

the low level circulation sweeps from continental China, along the lower mid-latitudes and subtropical north Pacific to the west coast of the U.S. The atmospheric path is also open at higher levels of the troposphere in winter. The Pacific jet stream crosses the north Pacific and reaches its greatest strength and farthest equatorward coverage during the boreal winter. Since the free troposphere westerly winds extend more to the south, they would also blow over Hawaii at these atmospheric levels. The linking of these distant regions through wind currents might therefore explain the nearly simultaneous annual peak of KD in Japan, Hawaii and San Diego.

In spring, the Aleutian low becomes much weaker and a strong high pressure develops in the subtropical north Pacific. At the same time, northwesterly winds are interrupted in Japan and the path across the north Pacific is redirected to even higher latitudes in the North Pacific. Similarly, in the free troposphere, the atmospheric path is much weaker and shifts more to the north in spring and summer. This springtime interruption coincides with the seasonal decline in KD cases in both San Diego and Hawaii.

Discussion

In this study, an examination of KD time series from three locations with high KD incidence, namely Japan, Hawaii and San Diego, revealed that a common seasonal increase in KD cases is associated with a large scale shift in the Asia-North Pacific wind pattern. This involves the wintertime development of a “duct” that sweeps from Asia to the western North Pacific and an associated trans-Pacific transport across the North Pacific from Japan to Hawaii and southern California. Other climatologic variables tested did not show the same degree of coherency with variations in numbers of KD cases as

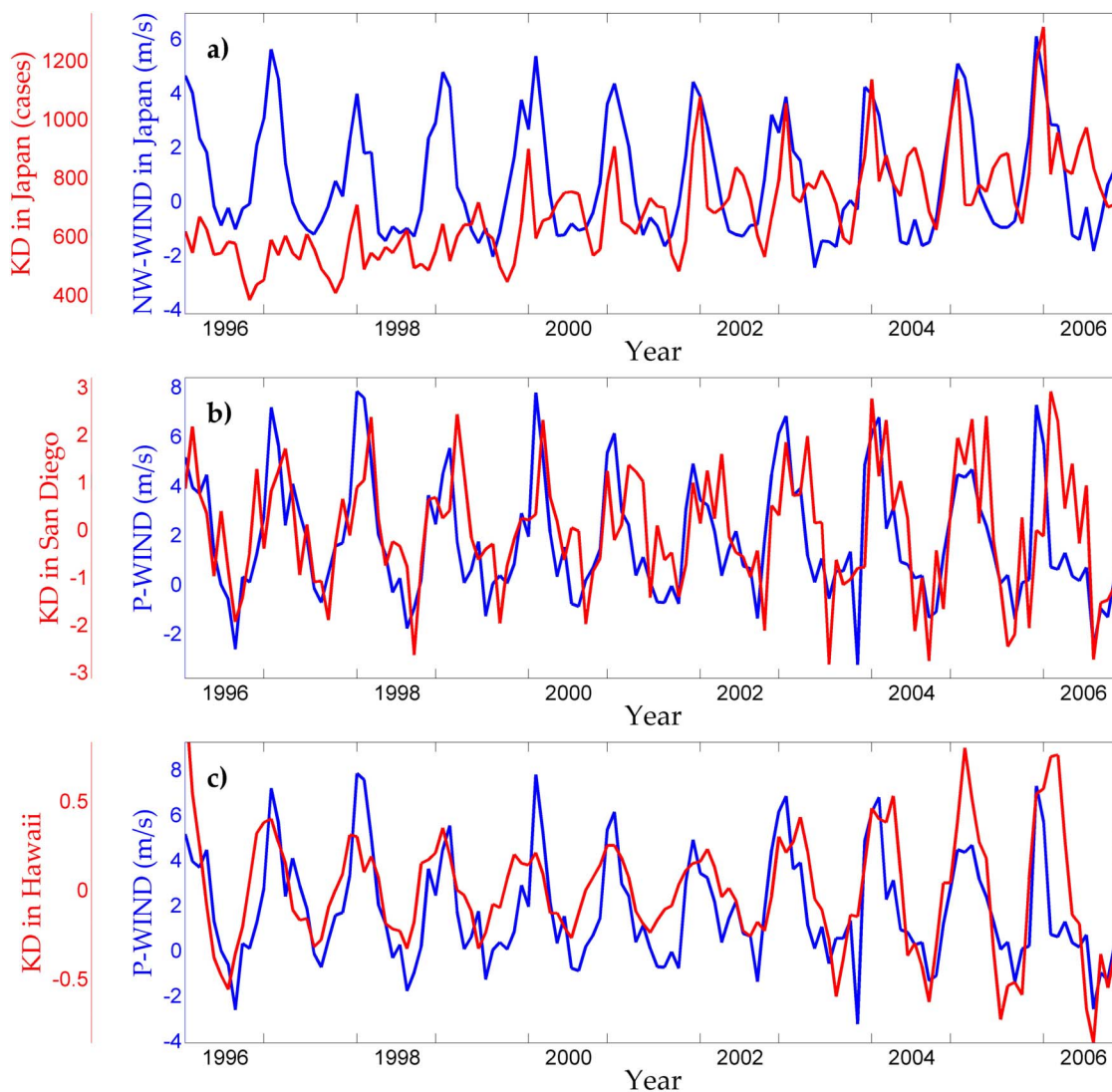


Figure 4 | KD and surface winds in Japan (a), San Diego (b) and Hawaii (c). Time series correspond to KD incidence (red lines in a, b and c), the northwestern component of surface winds in Japan (NW-WIND, blue line in a; m/s), and the Pacific Zonal Wind Index (P-WIND, blue lines in b and c; m/s). NW-WIND is defined as the projection of the horizontal two-dimensional wind onto a unit vector in the northwest/southeast direction (i.e. $\cos(45^\circ) \cdot \text{wind} - \sin(45^\circ) \cdot \text{vwind}$). P-WIND is defined as the mean zonal wind along 35°N between longitudes 140°E and 240°E (see the horizontal green line in Figures 5a,b). P-WIND is shown here for the surface level, but similar results were found for the middle and upper troposphere (e.g. Figure 5d). KD time series for San Diego and Hawaii are reconstructed components obtained after applying an eigendecomposition analysis to the KD data, to better isolate the annual component (see Methods). KD cases in Hawaii were accumulated prior to the eigendecomposition.

were found for wind and pressure patterns and therefore, did not pass cross-validation tests across sites and scales. The close timing of seasonal peaks in the three study locations, and the synchrony of these peaks with strong seasonal Asian and trans-Pacific wind patterns suggests that the causal agent of KD may be transported across the north Pacific by the strong air currents developing in the upper troposphere. Although the movement of an infectious agent on these wind currents would seem the most plausible explanation^{20–22}, the role of pollutants or other inert particles transported in these air masses should also be considered²³. Both hypotheses are currently being investigated.

The potential for an infectious agent to survive the conditions of low temperature ($< -40^\circ\text{C}$), low relative humidity ($< 30\%$ in the western north Pacific), and high ultraviolet exposure is clearly documented in the case of African dust particles harboring *Aspergillus sydowii* that is responsible for diseases affecting coral in the Caribbean²⁴. Many species of viable, UV-resistant bacteria have also been isolated from the upper troposphere²⁵ Although links between

human respiratory disease and large scale dust transport are well-documented, to date there has been no evidence of long-range wind transport of an infectious agent causing human disease²⁴.

From a practical point of view, results described in the present study suggest that it may be possible to predict KD activity, even without knowledge of the nature of the etiologic agent. The ability to forecast periods of increased disease activity in localized geographic regions would benefit physicians who must identify KD patients from among the hundreds of children with benign rash/fever syndromes²⁶. Forecasting of KD using the models presented here can be tested in areas of the northern hemisphere that are climatologically connected to the Asian continent through the free troposphere zonal westerly winds.

In summary, these novel results provide a testable hypothesis that the causal agent of KD is possibly distributed by the wind. These experimental predictions and the investigation of aerosolized microorganisms would provide a means to focus more narrowly the search for the etiologic agent.

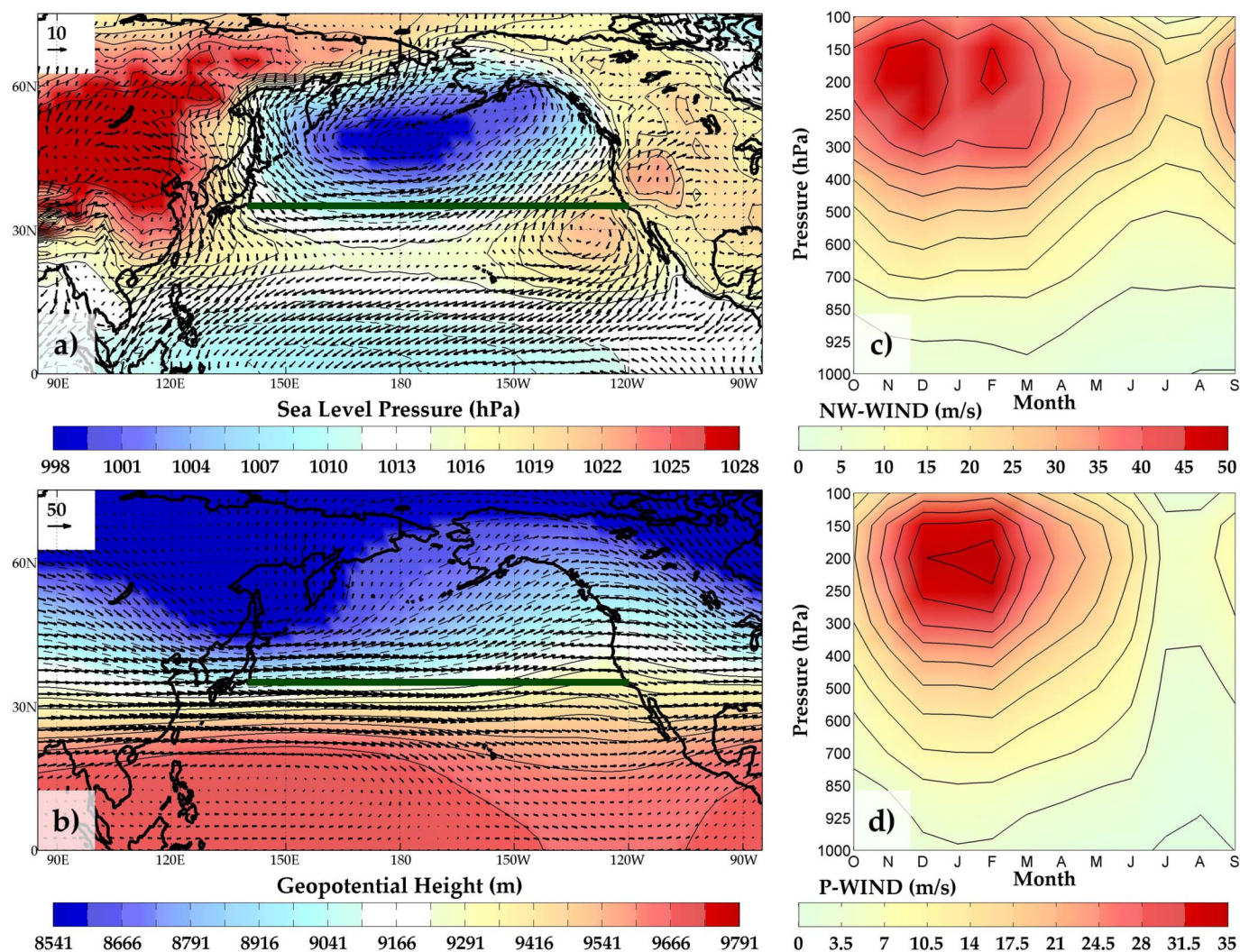


Figure 5 | Tropospheric winds in the North Pacific. Climatological January values are depicted for sea level pressure (hPa, a), surface winds (m/s, a), geopotential height at 300 hPa (m, b), and winds at 300 hPa (m/s, b). Panels c and d depict the seasonal cycle of the northwestern component of tropospheric winds in Japan (NW-WIND, m/s) and of the Pacific Zonal Wind Index (P-WIND, m/s), respectively. NW-WIND is here defined as the projection of the horizontal two-dimensional wind onto a unit vector in the northwest/southeast direction (i.e. $\cos(45^\circ) \cdot u_{\text{wind}} - \sin(45^\circ) \cdot v_{\text{wind}}$). P-WIND is defined as the mean zonal wind along the parallel 35°N between longitudes 140°E and 240°E (see the horizontal green line in panels a and b).

Methods

Time series of KD patients were gathered for Japan, Hawaii, and San Diego, three locations with high incidence of KD^{3,13,16}. In the three sites, the date of hospital admission was recorded for all subjects and, for subjects with multiple admissions, only the first hospitalization date was used. To provide uniform assessment among sites, the date of admission was used as a surrogate for the date of fever onset, even though for comparison with other studies, the average day of KD diagnosis is normally centered on the 5th day of fever. However, analyses were reproduced with calculated dates of fever onset and results did not differ (t-test, $p < 0.001$). The Japanese data set derived from 16 separate questionnaire surveys of hospitals in Japan. Spanning the period 1970–2008, it provides the most comprehensive record of KD cases in the world^{17–18} (Figure 1a). Data were analyzed for the 47 prefectures with a total of 247,685 cases over the 39-year period. Dates of hospital admissions for Hawaiian KD patients were obtained by review of hospital discharge diagnosis codes (ICD-9 code 446.1) for the interval 1996–2006 and totaled 498 cases. The time series for hospital admissions in San Diego was assembled from the database of the Kawasaki Disease Research Center at the University of California, San Diego. This database, spanning the period 1994–2008, captures more than 90% of the patients diagnosed with KD in San Diego County¹¹, and contained a total of 749 patients.

KD time series were decomposed into orthogonal frequency components^{27,28} and those significant components ($p < 0.01$) depicting variability at particular timescales were kept for further analyses (i.e. interannual in Figures 2a and 3a, annual and subannual in Figures 4b–c and Supplementary Figures 3b–c and 4; see also Supplementary Information for further details). The eigendecomposition analysis applied to the data covariance matrix, was used to partition signal contributions by frequency, with the aid of adaptive nonparametric functions²⁹. An embedding dimension or order of the decomposition of 40 was selected, as it allows a proper

characterization of signals of period higher than the year, for monthly data^{28,30}.

Of the three locations, only Hawaii did not exhibit a significant interannual component. Therefore, Hawaii was not included in the interannual analyses and only seasonality there was studied. Atmospheric data was derived from the NCEP/NCAR reanalysis^{31,32}.

High-frequency variability (i.e. periods shorter than 18 months) for the computation of spatiotemporal interannual atmosphere anomalies in Figures 2b–c, 3b–e and Supplementary Figures 2 was removed with the use of a recursive Butterworth filter³³. The significance test for these anomalies is based on a bootstrap method³⁴, and it is especially designed to compensate the decrease in the number of degrees of freedom as a result of the use of low-pass filters. For every grid-point (x, y) and time lag t (here from -18 to $+12$ months), let $value_{x,y,t}$ be the multi-peak mean anomaly that we want to test. Each $value_{x,y,t}$ is assigned to a statistical distribution generated according to a randomization test of 10001 permutations of local data in (x, y). Let $sample_{x,y,t} = \{s_0, s_1, \dots, s_{10000}\}$ be this sample distribution, with $s_0 \leq s_1 \leq \dots \leq s_{10000}$, used to test the significance level of $value_{x,y,t}$. Values within this distribution are then assigned to a percentile: $s_0 \rightarrow P_0, \dots, s_{5000} \rightarrow P_{50}, \dots, s_{10000} \rightarrow P_{100}$. The relative position of $value_{x,y,t}$ within the distribution is then calculated and a percentile within the distribution is assigned (i.e. $value_{x,y,t} \approx s_i \rightarrow P_{X_i}$). This procedure is repeated for every grid-point (x, y) and time lag t , and only values assigned to an extreme percentile are plotted as statistically significant. Here, only 5% of percentiles ($p < 0.05$) are considered to be extreme, being those the ones closer to P_0 (negative anomalies) or P_{100} (positive anomalies). Thus, following this conservative criterion, only 5% of data in the multi-peak composite evolution are shown as significant. A similar significance test can be found in other studies³⁵.

Screening of climatic variables that might correlate with KD across the different timescales and the three large epidemics, was performed at interannual timescales for



the following variables: geopotential height fields, zonal winds, meridional winds and vertical winds, all of them at 1000, 700, 500 i 300 hPa levels and horizontal winds at the surface, sea level pressures, sea surface temperatures, precipitation and land-surface temperatures.

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Author contributions

XR took the main role in the design of the study and performed analyses. JBa actively participated in the design of the study and performed analyses, JBu and DC actively participated in the design. JBu, MM, YN and RU provided the KD data for the different locations, ALL authors participated in the discussion of results and XR, JBa, JBu and DC wrote the manuscript.

Additional information

Supplementary information accompanies this paper at <http://www.nature.com/scientificreports>

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