Geographical distribution and spatio-temporal patterns of hospitalization due to dengue infection at a leading specialist hospital in Malaysia

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Abstract

Increasing numbers of dengue infection worldwide have led to a rise in deaths due to complications caused by this disease. We present here a cross-sectional study of dengue patients who attended the Emergency and Trauma Department of Ampang Hospital, one of Malaysia's leading specialist hospitals. The objective was to search for potential clustering of severe dengue, in space and/or time, among the annual admissions with the secondary objective to describe the spatio-temporal pattern of all dengue cases admitted to this hospital. The dengue status of the patients was confirmed serologically with the geographic location of the patients determined by residency, but not more specific than the street level. A total of 1165 dengue patients were included in the analysis using SaTScan software. The mean age of these patients was 27.8 years, with a standard deviation of 14.2 years and an age range from 1 to 77 years, among whom 54 (4.6%) were cases of severe dengue. A cluster of general dengue cases was identified occurring from October to December in the study year of 2015 but the inclusion of severe dengue in that cluster was not statistically significant (P=0.862). The standardized incidence ratio was 1.51. General presence of dengue cases was, however, detected to be concentrated at the end of the year, which should be useful for hospital planning and management if this pattern holds.

Introduction

An estimated 390 million dengue infections occur annually all over the world (Bhatt *et al.*, 2013). The World Health Organization (WHO) gives the figure of 500 000 people with severe dengue requiring hospitalization each year, about 2.5% of whom die (WHO, 2016). Various studies have investigated the geographical distribution of dengue outbreaks in countries where the disease is endemic. (Chang *et al.*, 2009; Anno *et al.*, 2015; Rotela *et al.*, 2017; Hafeez *et al.*, 2017). A few recent studies have also been conducted in Malaysia to evaluate the spatial pattern of the disease (Er *et al.*, 2010; Hassan *et al.,* 2012; Ling *et al.*, 2014). However, none of the studies focused on potential clustering of severe dengue cases as a way of limiting transmission.

The epidemiological pattern of dengue transmission has been studied for a long time and statistical modelling has been developed to predict future outbreaks (Louis *et al.*, 2014). Yet, public health interventions have not succeeded in interrupting transmission of the disease. Interventions such as fogging and larvae inspection in large areas, *e.g.*, all endemic parts of Malaysia, would require enormous manpower. However, the identification of clusters of severe dengue cases may help focusing public health interventions and thus make them more cost-effective. This approach may also provide predictive information on the specific risk factors, which depend on variations of the geographical landscape. Insights on severe dengue cluster patterns could be gained through the study of hospital admissions of dengue patients.

Understanding the development of dengue outbreaks

throughout the year is important for hospital planning and management, as appropriate resources are usually budgeted for and allocated annually from the central governing body, *i.e.* the Ministry of Health. Hence, the primary objective of this study was to investigate the occurrence of severe dengue clustering, in space and/or time during one year. The secondary objective was to describe the spatio-temporal pattern of all dengue cases admitted to the hospital in the same year. It was felt to be useful to carry out the work at Ampang Hospital, a leading specialist hospital located in an area endemic for dengue near Kuala Lumpur, the capital of Malaysia.

Materials and Methods

Study area and population investigated

This is a cross-sectional study of dengue patients attending the Emergency and Trauma Department of Ampang Hospital between February and December 2015. All data regarding dengue patients were obtained via the department's census record, which is the most reliable and complete source of data because all patients have to be registered in this department before being admitted or discharged. The Ampang Hospital provides health care services in

Figure 1. Ampang Jaya. Study area in pink with boundaries in red.

Ampang Jaya, a sub-district of Hulu Langat. The Ampang Jaya boundary and location is depicted in Figure 1. All cases beyond this boundary were excluded. Sporadic cases found outside Ampang Jaya were excluded because they are usually treated by other hospitals in surrounding subdistricts. Other excluded cases were people with addresses in other states of Malaysia or coming from other countries. All patients included in this study were confirmed positive for dengue infection, either due to the presence of dengue IgM antibodies or NS1 antigen or both. The enzyme-linked immunosorbent assay (ELISA) was used by the hospital laboratory to detect dengue IgM in the blood of patients suspected to be infected. The immunochromatographic NS1 Antigen rapid kit was employed in the Emergency Department and Medical Ward. (WHO/TDR, 2012) Patients were excluded if there was no positive dengue IgM or NS1 antigen test, or an equivocal result of the dengue IgM test had been obtained indicating uncertainty of status. The final diagnosis accepted was based on the clinical practice guidelines recommended by WHO in 2009 (WHO/TDR, 2012). The WHO 2009 classification sorts the disease into three subgroups according to the severity of the infection: dengue without warning sign, dengue with warning signs and severe dengue, which is further subcategorised into severe plasma leakage, severe bleeding and severe organ involvement. Only two diagnoses were utilized in this study: severe dengue and non-severe dengue (with and without warning signs).

Demographic data were extracted along with the corresponding home addresses, which indicated the geographic location of the patients. The longitude and latitude of these addresses were determined using Google Maps (2016 version). However, to ensure confidentiality, the addresses were not followed further than the street level. Therefore, the coordinates obtained using the addresses were only approximations of the exact locations. Addresses not found via Google Maps were obtained by travelling to their physical location and geocoded on site using Google Maps.

In Malaysia, *garden* is an area with a boundary somewhere between the street level and the district level. A total of 42 centroids, either representing a garden or a group of gardens, were coded. When areas had a particularly small geographical space, the centroids were coded together with adjacent areas. The list of the centroids and the corresponding geographical coordinates are tabulated in the Appendix.

Statistical analysis

Potential spatio-temporal clustering was investigated with space and time scan statistics using SaTScan software, v. 9.3 (Kulldorff, 2010). Briefly, SaTScan applies a circular scanning window centred on the geographic constituencies of the area under investigation (thus creating the centroid), which is allowed to gradually increase in size. Depending on the number of observed and expected cases within a centroid, *i.e.* window frame, as compared with the outside, a cluster of a disease may be pronounced. The decision of the existence of a cluster is made on the basis of a likelihood ratio test.

In this study, two statistical models were applied: the Bernoulli model and the space-time permutation model (Kulldorff, 2010). In the former, we investigated potential spatio-temporal clustering of severe dengue in relation to the spatio-temporal distribution of total dengue events. Severe dengue events were classified as *cases* and the non-severe dengue events as *controls*. The space-time permutation model was used to address the secondary objective of our study, *i.e.* the observed spatio-temporal distribution of all dengue

infections (both severe and non-severe) was compared to what would have been expected if the spatial and temporal distribution were independent to each other (*i.e.* without space-time interaction). This model included covariates such as age, gender and race that were used for adjustments.

In the spatio-temporal analyses, we set the range of 200 m as the maximum size of the spatial window radius and 14 days as the maximum temporal size. These parameters were set in accordance with the definition of dengue clusters in Malaysia (Malaysian Remote Sensing Agency, 2014). The mapping software of the epidemiological package of Epi Info 7 (Dean *et al.*, 2011) was used to display results in the form of maps. Google map was used to display the boundaries of the regions under investigation. The level of significance for all analyses was set at <0.05.

Results

The total number of dengue patients recorded by the Ampang Hospital during 2015 were 2379. Among them, 105 cases (4.4%) were severe dengue cases. There were 340 (14.3%) missing data. After excluding 874 cases originating outside the study area and the 340 missing data, our study group consisted of 1165 dengue patients, among whom 54 (4.6%) were classified as severe.

The mean age of the patients (ranging in age from 1 to 77 years) was 27.8 years with a standard deviation (SD) of 14.16. Upon stratification into severe and non-severe dengue, the mean age was 31.7 years (SD=14.33) and 27.6 years (SD=14.13), respectively. Information concerning gender, nationality and race, including laboratory confirmation and subclassification of severe dengue, is tabulated in Table 1. Most patients admitted to the hospital (100 patients) came from Pandan Indah. Each centroid code

Table 1. Included study subjects.

Attribute	Number of patients (%)		P-value*
	Non-SD**	SD**	
Gender			
Male	696 (59.7)	28 (2.4)	
Female	415 (35.6)	26 (2.2)	0.11
Nationality and race	Non-SD	SD	
Malay	590 (50.6)	28 (2.4)	
Chinese	191 (16.4)	11 (0.9)	
Indian	67 (5.8)	2 (0.2)	
Other Malaysians	11 (0.9)	1 (0.1)	
Non-Malaysians	252 (21.6)	12 (1.0)	0.88
Laboratory confirmation			
NS1 Antigen	139 (11.9)		
Dengue IgM	903 (77.5)		
Both NS1 Ag and dengue IgM	122 (10.5)		
Dengue virus genome detection***	1 (0.1)		
Sub-classification of severe dengue			
Severe plasma leakage	45 (83.3)		
Severe bleeding	1 (1.9)		
Severe organ involvement	6 (11.1)		
Unspecified	2 (3.7)		

*Chi-square test; **Severe dengue; *** Laboratory technical details of genome analysis was not available.

and population characteristic are tabulated in Table 2. The number of cases stratified by severe and non-severe dengue in each month between February to December 2015 is displayed in Figure 2.

Figure 3 displays the distribution of severe dengue cases among the non-severe ones in the study area. The SaTScan analysis using the Bernoulli model did not identify any severe dengue clusters (P=0.862), while the space-time permutation model revealed one statistically significant spatio-temporal cluster (P<0.001), *i.e.* cluster A centred on centroid 13 with a radius of 1.84 km which included the six neighbouring centroids 13, 8, 38, 9, 40 and 12. The time span of the cluster covered three months (October-December 2015). The standardized incidence ratio (SIR) was 1.89. After adjustment for age, gender and race, cluster A remained statistically significant (P<0.05) with the same time

Table 2. Population characteristics of each centroid.

Centroid	Code	Number of patients	Mean age (SD*)	Percentage of males
Kampung Tasik Permai	1	30	21.2(12.5)	56.7
Taman Dato Ahmad Razali/Ukay Heights	2	43	28.6(11.9)	79.1
Taman Melur/Taman Saga	3	21	33.3(17.3)	57.1
Pandan Indah	4	100	27.1(12.1)	60.0
Taman Komersial Pandan Indah	5	12	26.3(10.1)	83.3
Taman Shamelin Perkasa	6	24	26.3(8.5)	95.8
Wangsa Maju/Wangsa Melawati	7	7	31.6(24.6)	57.1
Pandan Perdana	8	46	29.0(13.5)	71.7
Taman Seraya	9	15	27.4(13.0)	53.3
Taman Cahaya	10	29	28.1(11.4)	69.0
Ukay Perdana	11	19	26.5(14.9)	47.4
Taman Kencana/Taman Lembah Maju	12	25	34.8(17.9)	52.0
Taman Cheras Utama/Cheras/Sri Bahtera	13	43	30.2(16.5)	74.4
Taman Angsana Hilir/Kampung Berembang/Kampung Perwira Jaya/Desa Pandan	14	36	25.0(12.1)	63.9
Kampung Pandan Dalam/Taman Nirwana/Taman Putra Sulaiman	15	69	25.2(14.3)	58.0
Taman Melawati/Taman Permata	16	13	27.5(12.2)	53.8
Taman Saujana Ampang/Taman Mulia	17	28	22.4(12.8)	57.1
Ampang Jaya/Kampung Melayu Tambahan/Taman Uda Jaya	18	20	29.0(15.4)	65.0
Kampung Baru Ampang/Taman Sri Merdeka	19	43	28.1(12.3)	55.8
Taman Ampang Mewah/Bandar Baru Ampang	20	44	31.0(14.2)	75.0
Pandan Mewah	21	32	25.3(13.7)	56.3
Taman Tasik Tambahan/Taman Sri Raya	22	24	23.9(17.1)	66.7
Kampung Ampang Campuran	23	13	22.4(15.9)	69.2
Taman Dagang/Taman Ampang Utama	24	16	32.4(16.4)	37.5
Taman Dagang Jaya	25	13	28.8(8.8)	53.8
Taman Mega Jaya/Taman Bukit Teratai	26	16	27.2(15.2)	68.8
Kampung Indah Permai/Lembah jaya	27	32	22.8(14.2)	56.3
Taman Bukit Indah	28	39	32.9(17.3)	56.4
Taman Cheras Indah/Taman Maju Jaya	29	19	29.3(12.1)	52.6
Taman Setiawangsa	30	24	31.0(14.6)	54.2
Kampung Berembang/Kuala Ampang	31	11	29.0(11.5)	54.5
Taman Keramat/AU 1/ AU 2	32	26	26.6(15.1)	53.8
AU 3/AU 4/AU 5/Taman Sri Ukay	33	32	28.7(12.6)	62.5
Taman Sri Watan/Taman Halaman/Taman Sri Ampang/Taman Bukit Ampang	34	30	26.4(16.5)	70.0
Taman Kosas	35	26	28.6(14.6)	69.2
Bukit Antarabangsa/Taman Bukit Mulia	36	14	33.9(17.0)	57.1
Taman Kelab Ukay/Sering Ukay/Taman Ukay Bistari/Zooview/Nusa Tropica	37	13	29.0(12.8)	53.8
Taman Bukit Permai/Bukit Pandan	38	18	29.9(15.4)	55.6
Taman Muda/Taman Mawar/Taman Putra	40	52	24.0(10.9)	71.2
Taman Cempaka/Taman Bakti Ampang	41	13	37.6(13.7)	53.8
Taman Pandan Jaya	42	35	29.1(16.7)	42.9

*Standard deviation.

span, still centred on centroid 13 but now with a radius of 1.73 km which included the same neighbouring centroids with the exception of centroid 12 (Figure 4). The SIR was 1.51. The characteristics of all clusters are displayed in Table 3.

Discussion

The occurrence of severe dengue cases followed the same spatial pattern as that of the non-severe dengue cases. This was supported by national statistical reports whereby the case fatality rate remained constant even though the total number of dengue cases was fluctuating between 2001 and 2016 (Malaysian Remote Sensing Agency, 2014). Although no statistically significant cluster of severe dengue cases was found, the secondary objective was successful, which should be useful for hospital planning and management. This concerns the statistically significant spatio-temporal cluster of general dengue infections discovered by the end of the study year. The presence of one or more severe dengue clusters was hypothesized because certain serotypes result in different outcomes of the disease (Soo *et al.*, 2016). Another hypothesis for the presence of severe dengue clusters is that the underlying genetic susceptibility of a population to the virus could play a role in the outcome of the infection (Khor *et al.*, 2011). Since the gene(s) making a person susceptible to severe dengue are hereditary, the possibility for a population to have the same susceptible gene(s)
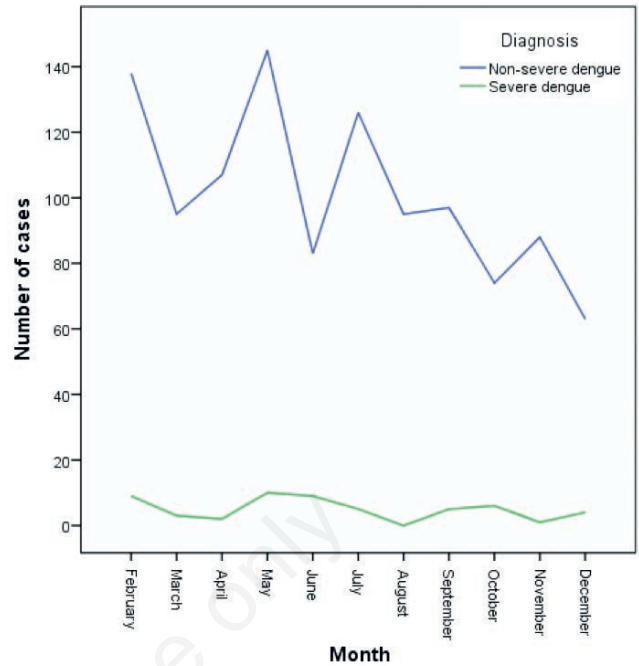

Figure 2. Annual review of the number of dengue cases admitted from Ampang Jaya per month in 2015.
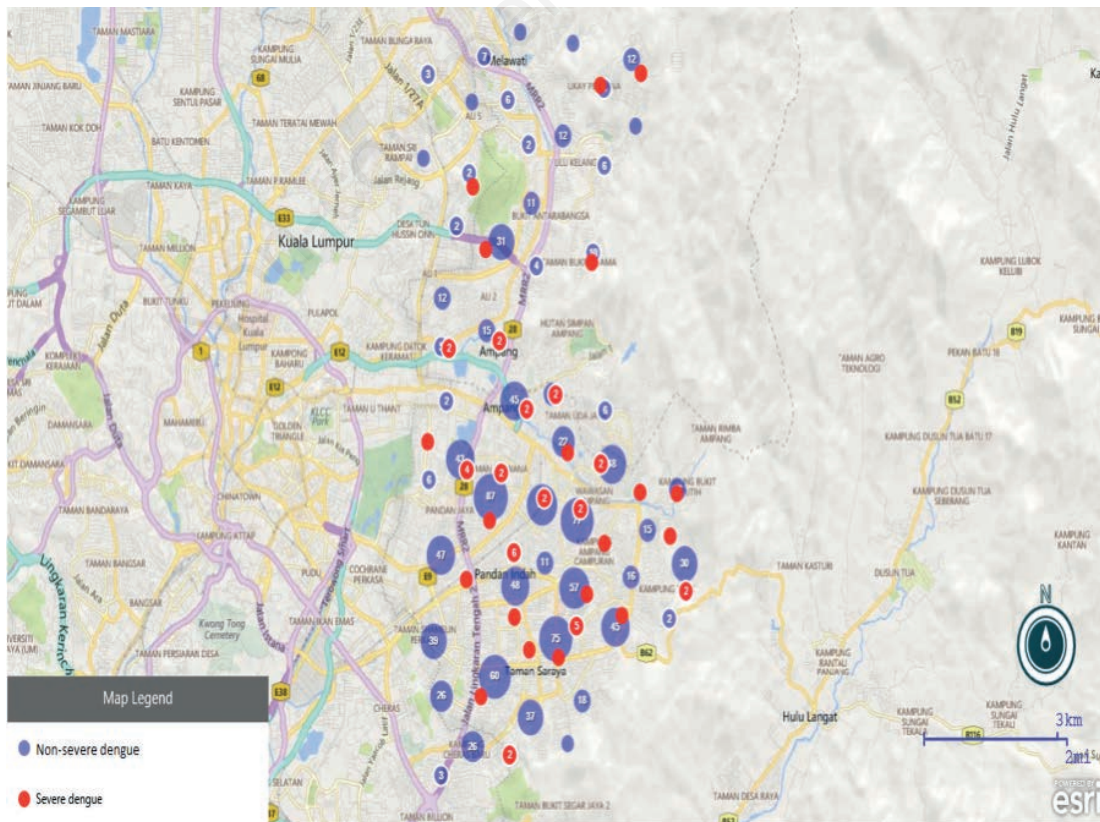

Figure 3. Distribution of severe dengue cases among the non-severe dengue cases.

increases. That our study failed to identify any such clustering might mean that different serotypes and susceptible genes do not play a significant role with regard to the geographical distribution of severe dengue.

Quite often only a single serotype of the dengue virus is responsible for an outbreak, which could also explain the absence of clustered severe dengue cases. In 2015, dengue serotype 1 was the predominant serotype (60%) circulating in Malaysia (WHO, 2015). This could imply that there is a complex host-virus interaction involving many other pathophysiological aspects of the disease with the clinical outcome not solely based on genetic factors (Coffey *et al.*, 2009; Htun *et al.*, 2015). Social health determinants, such as health-seeking behaviour, accessibility to healthcare as well as culture and socioeconomic condition, could all play a role
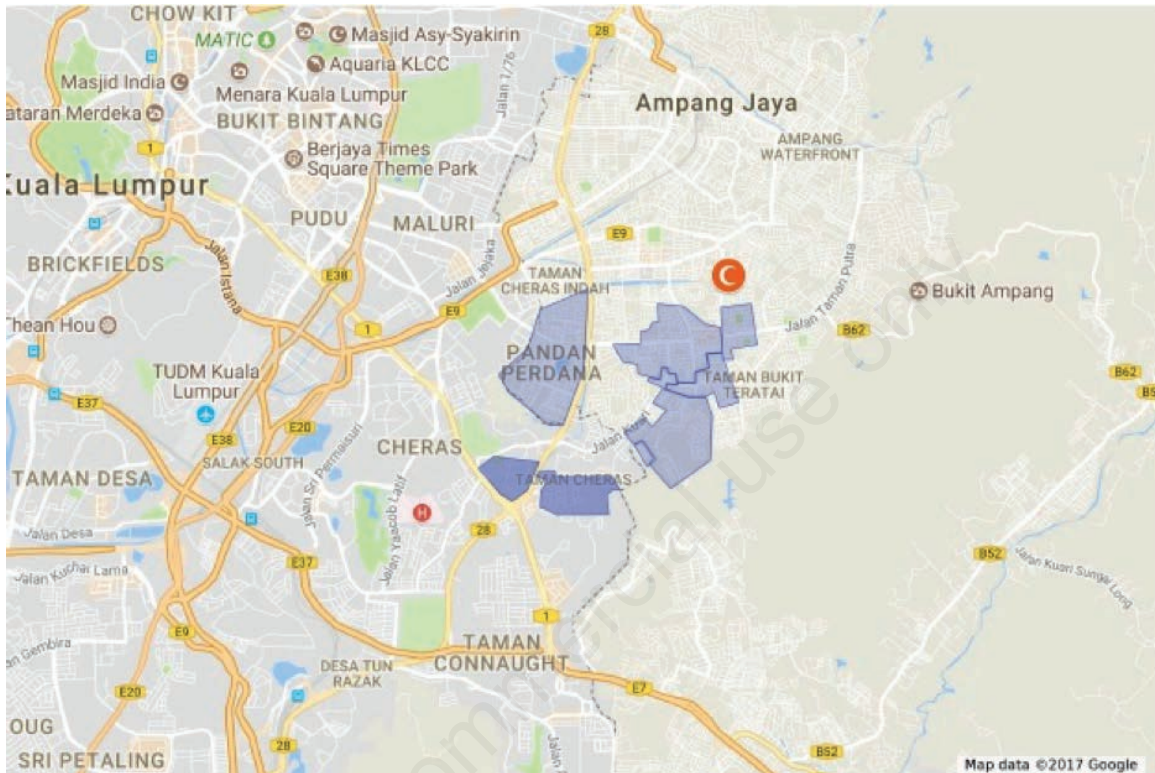

Figure 4. Cluster A with the five neighbouring centroids in relation to the location of Ampang Hospital. Legend: 🌙 **Ampang Hospital.**

Table 3. Characteristics of spatio-temporal clusters in the space-time permutation model.

Cluster	Centroid	Radius (km)	Time span	Number of locations	P-value	Observed cases	Expected cases	SIR*
Unadjusted								
A	13	1.84	October-December	6	<0.001	76	40.31	1.89
B	31	0.99	October-December	2	0.093	10	2.64	3.78
C	33	2.38	August-September	5	0.136	30	15.31	1.96
D	35	2.43	February-March	15	0.347	118	88.78	1.33
E	29	0.85	May	3	0.490	21	10.18	2.06
F	22	0.00	December	1	0.996	5	1.40	3.58
Adjusted (for age, gender and race)								
A	13	1.73	October-December	5	<0.05	68	45.03	1.51
B	30	0.00	August	1	0.103	7	1.86	3.76
C	31	0.99	October	2	0.160	10	3.60	2.78
D	20	2.14	February-April	16	0.326	197	164.99	1.19
E	29	0.85	May	3	0.954	21	12.66	1.66
F	16	0.00	April	1	0.999	4	1.25	3.21

*Standardized incidence ratio.

in the severity of dengue infection (Carabali *et al.*, 2015). These determinants could lead also to differences in the incidence of severe dengue among dengue-endemic countries. Since our study was limited to a single sub-district, shared traits of social determinants might have played a role in limiting clustering of severe dengue. Furthermore, treatment of dengue infection along with the WHO 2009 case classification (WHO/TDR, 2012) might have reduced the number of severe dengue cases as this approach was used to admit patients who had warning signs (WHO, 2009). Hence, treatment induced when the patient was admitted early to the hospital could have prevented the development of severe dengue and thus explain the steady low number of severe dengue cases per month even though the number of non-severe dengue cases fluctuated dramatically (Figure 2).

The single cluster detected at the end of the study year was not completely unexpected. Other studies report similar temporal clusters extending into the early months of the subsequent year since this time represents the rainy season in Malaysia (Aziz *et al.*, 2012; Ling *et al.*, 2014). However, the cluster found was different from other studies. The other studies were based on data obtained from district health departments, unlike our study which was hospital-based. In addition, our study was conducted much more recently than the others (Er *et al.*, 2010; Ling *et al.*, 2014). When adjusted for age, gender and race, this cluster (cluster A) consisted of five centroids in the time span of three months (October to December). The SIR observed for this cluster was 1.51 indicating that there was an excess of observed cases (23 cases) during this three-month period. Hence, there could be an outbreak of dengue cases between October and December in the following areas: Taman Cheras Utama, Cheras, Sri Bahtera, Pandan Perdana, Taman Bukit Permai, Bukit Pandan, Taman Seraya, Taman Muda, Taman Mawar, and Taman Putra that are all located south of Ampang Hospital. This location information could help first-aid responder services. Apart from gender, age and race, other covariates such as other demographic information, socioeconomic status and behavioural characteristics of the study population could also play a role affecting findings and possibly identify potential risk factor for the occurrence of the outbreak. With respect to potential limitations, deviation of coordinates from the actual resident of the patient could occur when the street level is used, particularly if there is a long road. However, the deviation should not be significant in our study because the majority of the roads within the centroids were short. Moreover, the random selection of coordinates along the road should not have altered the results significantly. Other limitation, such as population growth, could have affected the space-time permutation model if changes are not uniform throughout a study area. However, although our model did not include population data, the significance of population growth was negligible because the study only covered a single year. On the other hand, future studies employing a span of several years should consider changes in the population size.

The higher number of outbreaks at the end of the year detected among patients who visited Ampang Hospital, may be useful for hospital planning and management especially in allocating resources more effectively. Resources such as funding for treatment, manpower and the ambulance should be reserved for this possibility. However, the data need to be continuously analysed for a few years to be meaningful. Moreover, with a longer time of analysis, information useful for the prediction of outbreaks in the community served by the hospital may be found. The analysis can also be employed prospectively as the data are collected continuously.

Conclusions

The absence of clustered severe dengue cases may indicate that the occurrence of severe dengue cases may be spatio-temporally random in the population. However, the finding of increased number of general dengue cases during the three months at the end of the year should be useful in hospital planning and management. Prospective analysis might provide timely prediction of clustering of dengue cases. Emergency department may plan ahead in their emergency services including ambulance service.

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