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Emerging trends of malaria-dengue geographical coupling in the Southeast Asia region

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ABSTRACT

Background & objectives: Malaria and dengue fever are the most common mosquito-borne diseases in the Southeast Asia region (SEAR). We analysed a temporal record of annual cases of malaria and dengue fever from 1985–2009 in SEAR.

Methods: Data of dengue and malaria cases were obtained from WHO website for the period from 1985–2009. El-Nino Southern Oscillation (ENSO) fluctuation data were obtained from NOAA Climate Prediction Centre, Maryland. The wavelet analysis was conducted to analyse the data.

Results: Results showed that multiyear cycles of malaria outbreaks appeared in 1986 and 1996, concomitant with the timing of dengue cases at one year lag. The dynamics of both cases pronounce a regime shift in the 1999, when the coupling between dengue and ENSO is also stronger. The statistical significance of this coupling is evident from wavelet band-averaged cross power in 2–4 yr scale (95% confidence level).

Interpretation & conclusion: The present analysis suggests that the dengue incidence patterns in SEAR are periodic. There is not much evidence of malaria and ENSO having periodic association in the region; however, dengue fever and ENSO shows statistical significant cross-coherence in the 2–4 yr wavelet band and the results are statistically significant in the last decade. This study also provides statistical evidence of geographical clustering which quantitatively demonstrate the cross-country and cross-epidemic situations that exist across SEAR.

Key words ENSO; dengue; malaria; SEAR; wavelets

INTRODUCTION

Malaria and dengue fever are mosquito-borne diseases that severely affect public health worldwide[1]. These are recognised as serious impediments to economic and social development in the Southeast Asia region (SEAR)[2–12]. The two diseases are prevalent in tropical and subtropical countries. The mosquito vectors that transmit malaria have their main habitats in the forests, hills, foothills, irrigated wetland and rural periurban areas; whereas the main habitats of dengue vector are man-made breeding sources in urban areas. In SEAR, although cases of concurrent infections are scarce[13], statistical analysis of the comparative distributions of the two diseases is not well explored. It would be valuable to determine common periodic phenomenon between the two diseases. It is well known that the warm and moist climate conditions in the tropics are suitable for diseases like malaria and dengue and ideal breeding conditions for mosquitoes are provided during rainy seasons[14–16]. In this context, an important climatic factor is the El nino-southern oscillation (ENSO) phenomenon. The ENSO is a periodic interannual biphasic variation of atmospheric pressure and sea surface temperature (SST) in the equatorial Pacific Ocean. The ENSO controls local temperature and precipitation worldwide. The ENSO is known to have wide-ranging consequences on human health worldwide[17–18]. In this connection, several studies have observed the impact of ENSO on malaria and dengue in various countries[19–24].

The cross-correlation, cross spectra and related quantities provide information on possible links between different parameters[25–26]. In the present study, we assessed the relationship between malaria and dengue cases in SEAR. We also analyzed climate data, specifically ENSO, and examined its statistical association with malaria and dengue incidences. The wavelet analysis is a useful tool to interpret multiscale, non-stationary time-series data[27] and well suited for patterns of variability that change with time, such as transient cycles, allowing the identification of not only dominant periods but also their timing in the epidemiological data[28]. The wavelet methods have been widely used to analyse relationship between ENSO and dengue incidence to identify time- and frequency-associations[29–30]. These are known to be multiyear variations in dengue incidence; however, their association with ENSO has reported to be varying in different geographical locations. For example, in Mexico, no association is observed, whereas in Puerto Rico, statistically significant correlation is reported between ENSO and dengue incidence[29]. The wavelet analysis has been used to establish associations between the multi-annual components of dengue incidence and ENSO in Thailand[30]. Although, many of the wavelet based studies have analysed ENSO association with Asian countries, a comprehensive study on SEA region is sparse. The present study is one of the first attempts to explore malaria-dengue-ENSO statistical association in the SEA region using the wavelets.

MATERIAL & METHODS

The set of data analysed in our work includes the time-series of malaria and dengue reported cases which are used to show epidemiological trends overtime. The SEAR includes eleven countries namely, Bangladesh, Bhutan, DPR Korea, India, Indonesia, Myanmar, Maldives, Nepal, Sri Lanka, Thailand and Timor-Leste. The data on reported cases of malaria and dengue fever in SEAR individual countries were obtained from the World Health Organization website. The total number of cases in SEAR is the sum of all individual SEAR countries. All the data used in the present work are annual and cover the period from 1985–2009. The malaria cases from Maldives are not included in the study as malaria is not a public health problem there. Similarly, there are no reported cases of dengue fever in Korea, hence, these are not included.

The data set contains time series of SST anomalies, which are indicative of ENSO fluctuations. The data are taken from the NOAA Climate Prediction Centre at the website from: *http://www.cpc.ncep.noaa.gov/data/*.

Wavelet analysis

The wavelet analysis involves transformation of a data series with a wavelet, a localized wave. The data are transformed into the frequency domain, in which periodic behaviour is more easily analysed. The wavelet transform analysis provides a tool well suited to the study of multiscale, nonstationary processes over finite spatial and temporal domains and has found applications for time-series signal detection and analysis. Continuous wavelet transform is a common tool for analyzing localized intermittent oscillations in a time-series. It is important to examine two time-series together. In particular, to examine whether regions in a time frequency space with large common power have a consistent phase relationship and, therefore are suggestive of causality between the time-series.

For a discrete sequence, X_n, $n = 0, \ldots, (N-1)$, the continuous wavelet transform $W_n^x(s)$ is defined as a convolution of with a scaled and translated version of a wavelet function φ

$$W_n^x(s) = \Sigma_{n'=0}^{N-1} X_n \varphi^* \left[\frac{(n'-n)\delta t}{s}\right] \quad \ldots (1)$$

where, *denotes the complex conjugate, δt is the (sampling) time interval between two consecutive points in the time-series and s is the wavelet time scale which provides a measure of the width of ψ in time. We select for the present work the Morlet function.

$$\varphi(\eta) = \pi^{-1/4} e^{-\omega o} \eta e^{-\eta^2/2} \quad \ldots (2)$$

where, ω_0 is a nondimensional frequency, taken equal to six in order to satisfy the wavelet admissibility condition[27], and η is a nondimensional time parameter. The wavelet function in each scale is normalised to have unit energy.

$$\Sigma_{-\infty}^{\infty} \left|\hat{\Psi}(\omega)\right|^2 d\omega = 1 \quad \ldots (3)$$

$$W_n^{XY}(s) = W_n^x(s)\left[W_n^Y(s)\right]^* \quad \ldots (4)$$

For the present analysis, it turns out that the most revealing quantity to consider is what we shall call the band-averaged wavelet power $R_b^x(t)$, which is a weighted sum of the wavelet power spectrum over a given band of scales in the form proposed by Torrence and Compo[27].

$$R_b^x(t) = \frac{\delta j \delta t}{c_\delta} \Sigma_{j_1}^{j_2} \frac{\left|w_n^x(s_j)\right|}{s_j} \quad \ldots (5)$$

where, $s_j = s_o 2^{j\delta j}$, $j = 0, 1, \ldots, J$, and $J = \delta_j \log_2 (N\delta t/s_o)$. Here $s_o = 0.5$ yr as we work on yearly data. For the interval δ_j, the largest value that still gives a resolution small enough for wavelet power to appear smooth in time is 0.5 yr in case of the Morlet wavelet[27]. In the present case, we have found it useful to choose $\delta_j = 0.25$ yr in order to obtain finer resolution in scale. The constant $c_\delta = 0.776$ is a scale-independent reconstruction factor for the Morlet function.

It is crucial to assess the statistical significance of the periods exhibited by the wavelet approach. The details of the method can be found in 'a practical guide to wavelet analysis'[27].

Hierarchical clustering

Clustering is grouping of objects based on their degree of similarity. Various methods have been proposed for data clustering in diverse scientific fields[31–32]. In the present study, hierarchical clustering was used in order to classify correlated malaria and dengue condition in SEAR countries. The details of the method can be found elsewhere[32–33].

RESULTS & DISCUSSION

We began by characterizing the dominant temporal patterns present in the time-series of malaria and dengue cases (1985–2009). We found that the burden of malaria in SEA region was much higher than dengue in the time-series data under study. For instance, in 2010, 1.6 million cases of malaria were reported in India, whereas dengue cases were 9357. The malaria epidemic is deeply rooted in the poor communities, particularly among those living in remote forest areas such as tribal populations. This is the reason that there is a much higher incidence of malaria than dengue in SEAR. To observe the temporal patterns, the normalized data (zero mean and unit standard deviation) of malaria and dengue cases for SEAR are plotted in Fig. 1. It is clear from the Fig. 1 that during the last decade (1999–2009), there has been a dramatic decline in the trend of malaria, while the prevalence of dengue fever is increasing. The decrease in malaria cases can be attributed to the growing international awareness and funding that has led SEAR to make new efforts towards controlling malaria. The malaria mortality has declined in all countries presumably due to use of artesunate combination therapy (ACT), insecticide-treated mosquito nets (ITNs), indoor-residual spraying (IRS), long-lasting insecticide-treated nets (LLINs), and other effective interventions. Whereas, the incidence of dengue fever shows an increasing trend in recent years due to globalization, population growth and uncontrolled urban development.

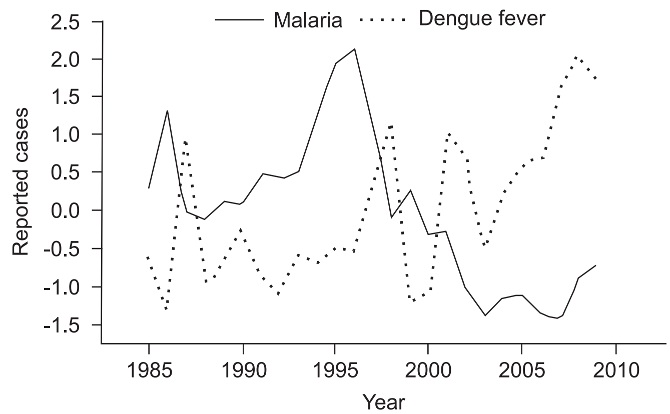


Fig. 1: The normalised reported cases of malaria and dengue fever in SEAR (1985–2009).

The Pearson's correlation coefficient between the two time-series is calculated as -0.63 ($p < 0.05$). It showed that both the diseases are inversely correlated. Figure 1 shows that the multiyear cycles of malaria outbreaks appear in the years 1986 and 1996, concomitant with the timing of dengue cases at one year lag. Nevertheless, we found that the correlation is higher in the last decade (1999–2009), where the two appear to be in anti-phase (Pearson's correlation coefficient -0.47). This variation in malaria and dengue transmission is likely to depend on environmental and socioeconomic factors.

The Pearson's correlation coefficients between malaria and dengue cases for SEAR individual countries are shown in Table 1. To study the confidence levels of estimated correlation coefficients we computed *p*-values to test the confidence levels. Table 1 show that malaria and dengue are significantly positively correlated in Indonesia, Myanmar and Timor-Leste, whereas malaria and dengue are negatively correlated in rest of the countries under study.

Table 1. The cross-correlations between SEAR countries

SEAR/ countries	Corr. coef. between malaria and dengue	Corr. coef. between malaria and ENSO	Corr. coef. between dengue and ENSO	Wavelet periods between malaria and dengue (Significant 95%)	Wavelet periods between malaria and ENSO (Significant 95%)	Wavelet periods between dengue and ENSO (Significant 95%)
SEAR	−0.63	0.14	− 0.03	2–4 yr	None	2–4 yr
Bangladesh	−0.22	0.22	− 0.01	None	None	2–4 yr
Bhutan	−0.25	0.31	0.097	None	None	2–4 yr
Korea	Nil	− 0.18	Nil	Nil	None	Nil
India	− 0.51	0.15	− 0.18	2–4 yr	None	2–4 yr
Indonesia	0.85	− 0.33	− 0.33	None	None	None
Maldives	Nil	Nil	− 0.17	Nil	Nil	None
Nepal	− 0.33	0.12	− 0.19	None	None	None
Myanmar	0.70	− 0.35	− 0.015	None	None	2–4 yr
Sri Lanka	− 0.56	0.30	− 0.15	None	None	None
Thailand	0.15	− 0.008	0.36	None	None	2–4 yr
Timor-Leste	0.58	− 0.18	0.05	None	None	2–4 yr

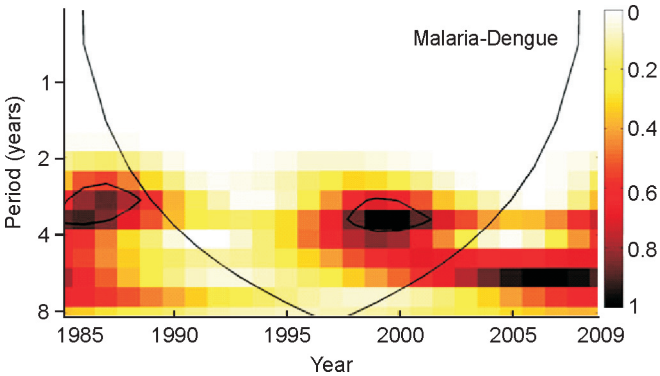
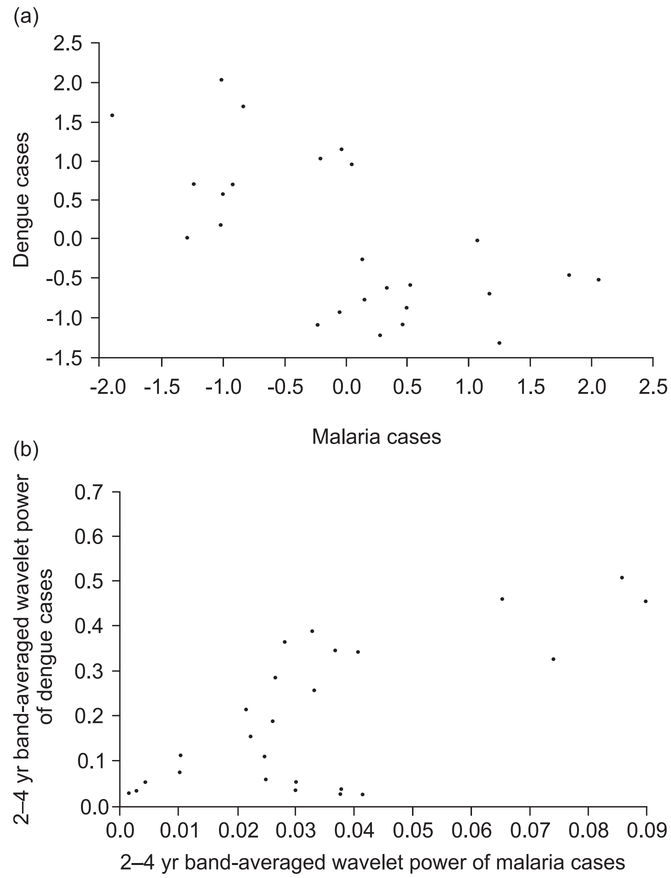


Fig. 2: Wavelet cross-power spectrum of malaria and dengue cases in SEAR.

In order to investigate whether a more direct association between malaria and dengue cases (in SEAR) can be established, we present a wavelet analysis in the form of colour-coded contour maps of wavelet power spectra as functions of time and Fourier period (henceforth referred to as period). Figure 2 shows the map of wavelet cross-power spectrum between malaria and dengue cases in SEAR. Outlined on these graphs are contours enclosing regions where wavelet cross power is significantly higher, at 95% confidence level with respect to the reference spectra. It is seen that there is a high cross power in the 2–4 yr period band and it is statistically significant over 1998–2000.

The plot of the raw time-series of malaria and the dengue cases are shown in Fig. 3. The plot exhibits a lot of scatter for which the correlation coefficient is found to be – 0.63 between the two raw time-series (95% confidence band). To investigate the plausible presence of harmonics in malaria and dengue cases, the 2–4 yr band-averaged wavelet coefficients are plotted in Fig. 3 (b) for SEAR. This, suggests that a relatively well-defined relationship between the malaria and the dengue is evident (correlation +0.70, $p<0.05$) only at the shorter time scales.

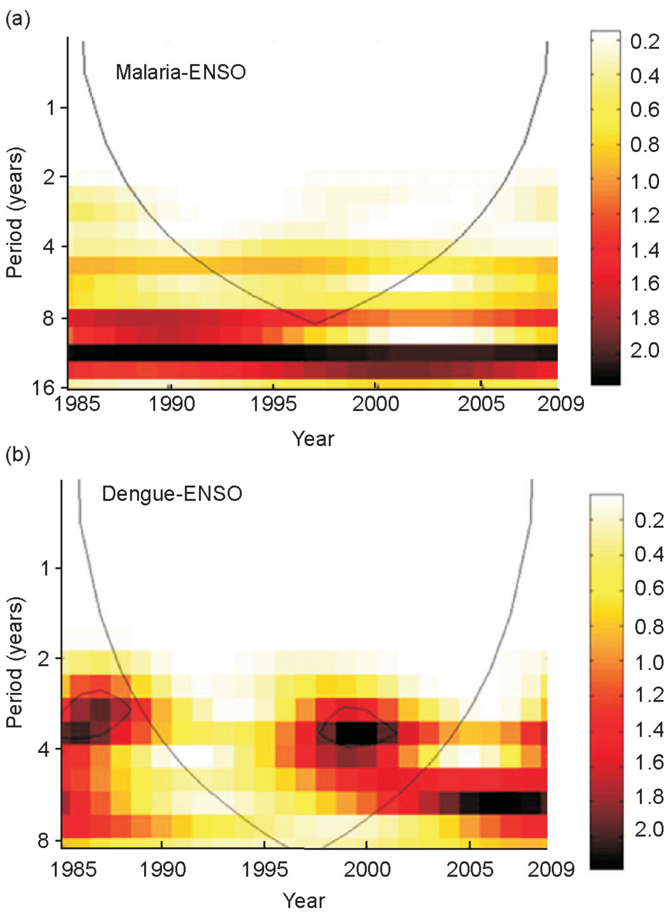
In order to investigate the statistical relation of malaria and dengue cases with ENSO in SEA region, Pearson's correlation coefficients between malaria and dengue, and ENSO are listed in Table 1. The correlation coefficient between malaria cases and ENSO in SEAR is, 0.14. If we see these correlations in individual countries, it is positive in Bangladesh, Bhutan, India, Nepal and Sri Lanka; whereas, it is negative for rest of the countries under study. On the other hand, the correlation coefficient between dengue cases and ENSO in SEAR is – 0.03 which goes with the earlier work reported elsewhere[33] where a negative correlation between the ENSO indices and dengue is observed in Costa Rica. If we discern these correlations in individual countries, it is negative in Bangladesh, India,



Figs. 3 (a & b): Normalised malaria and dengue cases (a); and 2–4 yr band-averaged wavelet power of malaria and dengue cases (b) in SEAR.

Indonesia, Maldives, Nepal, Myanmar and Sri Lanka; whereas, it is positive for rest of the countries under study.

Figure 4 shows the wavelet cross power spectra of dengue-ENSO and malaria-ENSO for SEA region. Figure 4 (a) shows that there is no significant period between malaria and ENSO in SEAR. Also, Table 1 shows that this association is not evident in any of the individual countries. Whereas, Fig. 4 (b) shows that the 2–4 yr period band exhibits predominantly the highest cross wavelet power. Hence, Fig. 4 (b) shows that there is a correlation between El Niño and dengue cases in SEAR during 1985–1988 and 1999–2002. However, the power of these cycles is more intense or statistically significant at the 95% confidence level during 1999–2002 since, it lies inside the 'cone of influence' and is therefore considered significant. These common periods are evident in Bangladesh, Bhutan, India, Myanmar, Thailand and Timor-Leste as shown in Table 1. In the literature, wavelet analysis has been performed on Thailand to establish a relationship between dengue and ENSO which is in good agreement with the present findings[30]. Therefore, ENSO can be used as an early warning system for dengue in



Figs. 4 (a) & (b): Wavelet cross-power spectrum of; (a) malaria cases and ENSO; and (b) dengue cases and ENSO in SEAR.

SEAR. Fuller *et al*[31] have reported interesting results to predict dengue using ENSO in Costa Rica. Their model could be able to predict dengue outbreaks as early as 40 wk in advance[31].

In the above sections we have investigated the statistical association between malaria and dengue fever cases in SEAR and individual countries. To assess distinct cross-country links in the distribution of these epidemics and the possible reasons behind such association, we apply a clustering technique defined in section 2 over the time period from 1985–2009. Figure 5 shows a *dendrogram,* which clusters malaria and dengue grouping in all the countries under study. The cophenetic coefficient calculated with the *dendrogram* has a reasonably high value indicating that the cluster information generated by the *dendrogram* is a good representation of similarities in the data. The horizontal axis in Fig. 5 presents SEAR countries under study, and the vertical axis indicates separation (or 1-correlation) between them. In Fig. 5, endemic SEAR countries are classified into distinct clusters (at 0.6 separation level), which demonstrate cross-country cross-disease statistical classification. In cluster one, Nepal, Thailand, Sri Lanka, Bangladesh, Bhutan and India malaria cases form one homogeneous group. We now compare the similar characteristics of individual countries in this cluster. It is reported by WHO that malaria incidence (confirmed cases) has reduced by >50% in the Nepal, Thailand, and Sri Lanka which come together in cluster 1 in the present study. This is due to the fact that recently there has been a renewed emphasis on malaria vector control with IRS and the countries under cluster 1 are reported to have achieved 100% coverage. In fact, of the 10 malaria-endemic countries in the region, Sri Lanka has

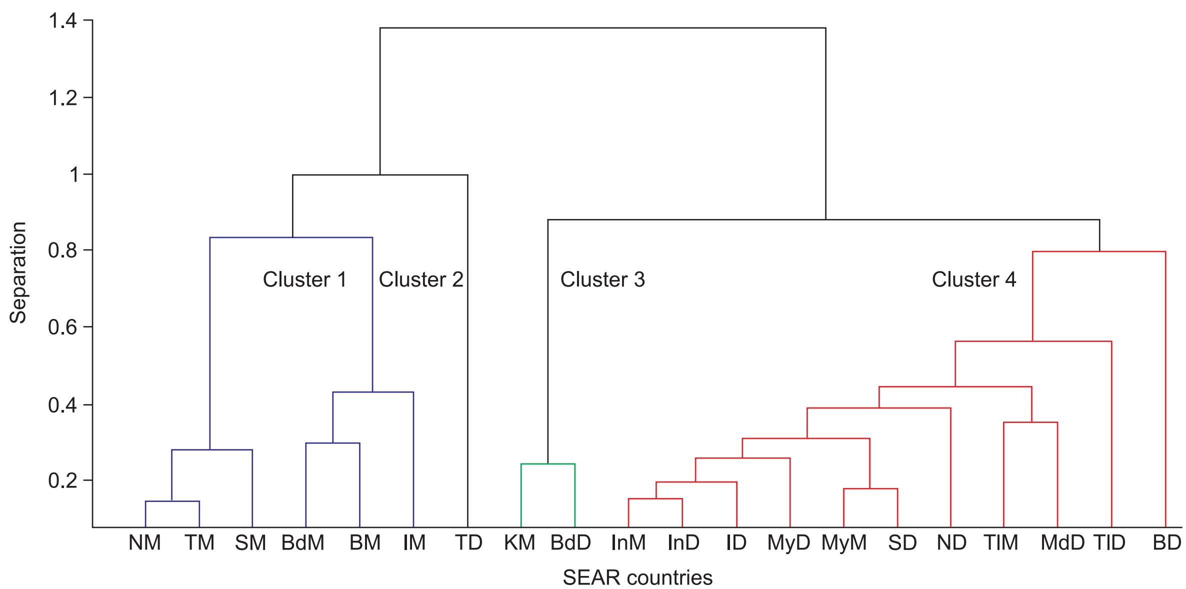


Fig. 5: Dendrogram representing the hierarchical clustering of malaria (M) and dengue (D) cases across SEAR countries over the time period (1985–2009); N–Nepal; Md–Maldives; T–Thailand; S–Sri Lanka; Bd–Bengladesh; B–Bhutan; I–Indonesia; In–India; K–Korea; Tl–Timor-Leste; My–Myanmar.

reached the malaria pre-elimination stage whereas two other countries, Nepal and Thailand, have made good progress in this direction. Figure 5 shows that Nepal and Thailand malaria cases have minimum separation, hence are highly synchronised (correlation coefficient 0.85) in the cluster. Also, it comprises two neighbouring countries Bangladesh and Bhutan, where the highest reduction in malaria mortality cases were recorded by WHO. In cluster 2, dengue in Thailand stands alone. In cluster 3, malaria in Korea and dengue in Bangladesh are highly correlated with correlation coefficient 0.75. The remaining countries under study form the cluster 4 as shown in Fig. 5. In Indonesia, malaria and dengue cases are highly correlated with correlation coefficient of 0.85. Similarly, the malaria cases in Myanmar and dengue cases in Sri Lanka are correlated with correlation coefficient of 0.75; Timor-Leste's malaria cases and Maldives' dengue case are correlated with correlation coefficient of 0.65.

It is reported by WHO that the number of dengue fever cases have been rising since 2003 in SEAR. Thailand reported the highest number of dengue cases in the region till 2003; from 2004 onwards Indonesia reported highest number of dengue cases in the region. In 2006, Indonesia reported 57% of the dengue cases in the region. The three countries in cluster 4 namely, Indonesia, Myanmar and Sri Lanka have established National Dengue Prevention and Control Programmes. Although India and Maldives do not have National Dengue Control Programmes, they have undertaken vector-borne disease control/malaria control activities for emergency control of epidemics. These clustering showed similar patterns among SEAR countries. However, intra-cluster similarities are due to various direct and indirect factors that influence emergence of epidemic. Therefore, the biology and ecology of vectors as well as social and socioeconomic factors in different countries require to be investigated in more detail to establish inter-country relationships.

CONCLUSION

We investigated the statistical relation between malaria and dengue cases in SEA region and its individual countries over the time period from 1985–2009. We first analyzed the direct association between malaria and dengue reported cases. The correlation coefficient between malaria and dengue cases is – 0.63 and both the time-series are in antiphase in the last decade. However, a relatively well-defined relationship between malaria and dengue is evident (correlation +0.70) only at the shorter wavelet scales. Indeed, in wavelet domain both the time-series exhibit cross-coherence (95% statistically significant in last decade) and the same is observed in case of dengue and ENSO.

This study also provides statistical evidence of geographical clustering which quantitatively demonstrate the similar situations that exist between endemic countries across SEAR. It is concluded that malaria and dengue are significantly positively correlated in Indonesia, Myanmar, and Timor Leste. We also investigated that cross-country cross-disease links, for example, malaria in Korea and dengue in Bangladesh; malaria in Myanmar and dengue in Sri Lanka; malaria in Timor-Leste and dengue in Maldives are significantly correlated. Such classification can provide guidelines for resource utilisation in integrated control of diseases. Also, the situation of an epidemic in various countries varies greatly from year to year. A technique like cluster analysis can be very useful in identifying the long-term patterns.

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