Regime shifts and heterogeneous trends in malaria time series from Western Kenya Highlands

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SUMMARY

Large malaria epidemics in the East African highlands during the mid and late 1990s kindled a stream of research on the role that global warming might have on malaria transmission. Most of the inferences using temporal information have been derived from a malaria incidence time series from Kericho. Here, we report a detailed analysis of 5 monthly time series, between 15 and 41 years long, from West Kenya encompassing an altitudinal gradient along Lake Victoria basin. We found decreasing, but heterogeneous, malaria trends since the late 1980s at low altitudes (<1600 m), and the early 2000s at high altitudes (>1600 m). Regime shifts were present in 3 of the series and were synchronous in the 2 time series from high altitudes. At low altitude, regime shifts were associated with a shift from increasing to decreasing malaria transmission, as well as a decrease in variability. At higher altitudes, regime shifts reflected an increase in malaria transmission variability. The heterogeneity in malaria trends probably reflects the multitude of factors that can drive malaria transmission and highlights the need for both spatially and temporally fine-grained data to make sound inferences about the impacts of climate change and control/elimination interventions on malaria transmission.

Key words: time series, breakpoint, *Plasmodium*, Kericho, Kapsabet, Kisii, Kisumu, Maseno, Kendu Bay, climate change, seasonal autoregressive.

INTRODUCTION

Large malaria epidemics in the East African highlands during the mid and late 1990s triggered a number of inquiries into the role that global warming might have on malaria transmission. Several authors proposed that spread of malaria into areas that rarely saw malaria transmission could be related to the impacts that small increases in temperature have on *Plasmodium* spp. development inside vectors (Lindsay and Birley, 1996; Patz and Olson, 2006). Traditionally considered a 'malaria-free' oasis inside a desert of high malaria transmission, the East African highlands are of special interest because of their geographical location (Lindsay and Martens, 1998). In particular, the role that climate change could have played on exacerbated malaria records in this area over recent years has been the focus of intensive research and debate (Chaves and Koenraadt, 2010).

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Studies from highland areas in Ethiopia, Tanzania, Kenya and Uganda have robustly shown signatures of climatic covariates on malaria time series (Abeku *et al*. 2004; Chaves and Koenraadt, 2010; Teklehaimanot *et al*. 2004; Zhou *et al*. 2004). A great deal of attention has been given to whether oscillations in the time series were intrinsically generated i.e., by the cyclic nature of immunity in growing populations (Hay *et al*. 2000), or were induced by exogenous factors (Pascual *et al*. 2008; Childs and Boots, 2010) and drug resistance (Artzy-Randrup *et al*. 2010). In addition, some studies have claimed to show that trends in temperature have driven the surge observed in transmission over recent years (Alonso *et al*. 2011). However, little attention has been given to the homogeneity/heterogeneity in transmission trends across the East African highlands, especially as revealed by time series analysis. In fact, most time series analyses have been exclusively focused on a time series from Kericho in Kenya (Hay *et al*. 2000; Hay *et al*. 2002*a*; Shanks *et al*. 2000, 2002, 2005; Pascual *et al*. 2008; Artzy-Randrup *et al*. 2010; Childs and Boots, 2010; Alonso *et al*. 2011). Several cross-sectional studies that examined transmission patterns across altitudinal gradients in the East African highlands reported an overall decrease in

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transmission with altitude (Bødker *et al*. 2003, 2006; Drakeley *et al*. 2005). Similar studies looking at several time series have tended to use coarsely grained data, for example, records from districts (Abeku *et al*. 2004; Teklehaimanot *et al*. 2004), hospital time series from distant locations (Zhou *et al*. 2004) or have mixed inpatient data, i.e., virulent cases admitted to a hospital, with outpatient data, i.e., febrile cases that visit the hospital but require no further attention in a hospital and not parasitologically confirmed (Zhou *et al*. 2004; Pascual and Bouma, 2009). Others have focused on showing the signatures of large-scale climatic phenomena such as the Indian Ocean Dipole (IOD) Mode on malaria transmission (Hashizume *et al*. 2009). However, further inquiries into the homogeneity of these trends, for example, whether the incidence is similarly increased or decreased through time, or is dependent on the existence and synchronicity of regime shifts, i.e., whether similar abrupt changes on the average and the variability of malaria incidence have been simultaneously observed in East Africa, has been out of the research agenda.

Here, we employ 5 time series from hospitals in the Lake Victoria basin region of Western Kenya, an area with well-defined and regionally homogeneous seasonal climatic patterns (Anyah and Semazzi, 2004; Anyah *et al*. 2006), and ask whether these time series show similar regime shifts. We also ask whether increasing transmission trends reported for Kericho (Shanks *et al*. 2000) are common to the whole Lake Victoria basin. We found that regime shifts, when present, were asynchronous along the altitude range but synchronous at high altitude. Trends in the time series also changed with altitude. At low altitudes, i.e., below 1500 m, malaria incidence began to decrease in the late 1980s. By contrast, the variability and average of malaria transmission either kept constant or increased at higher altitudes, above 1600 m, especially during the 1990s, and began to decrease in the early 2000s. Finally, our results highlight the need for both spatially and temporally fine-grained data to make sound inferences about the impacts of climate change and control/elimination interventions on malaria transmission.

MATERIALS AND METHODS

Data

Figure 1A shows the location of our study sites within Lake Victoria basin and the elevation range that they span. Time series data used in our study are monthly records of inpatients diagnosed with malaria in Maseno (Fig. 1B), Kendu Bay (Fig. 1C), Kisii (Fig. 1D), Kapsabet (Fig. 1E), Kericho (Fig. 1F). Figure 1 also shows monthly rainfall records for Kisumu (Fig. 1G), Kisii (Fig. 1H), Kapsabet (Fig. 1I), Kericho (Fig. 1J) and the dipole mode index (DMI, Fig. 1K) and El Niño 3 (ENSO, Fig. 1L). The 5 malaria time series are monthly counts of inpatients admitted into the hospitals because of high fever and other clinical malaria symptoms. In Kericho, all malaria cases where confirmed by blood-slide examination (bse) (Hay *et al*. 2000; Shanks *et al*. 2000, 2002, 2005). In the other 4 sites (Maseno, Kendu Bay, Kisii and Kapsabet) we collected the data from books with malaria-diagnosed inpatient records. Unfortunately, these books did not indicate whether all recorded malaria cases were confirmed by bse. We were informed by staff members from each hospital that cases were often confirmed by bse, but hospital staff members were unable to guarantee a confirmation of all cases by such a method. However, in each hospital, staff members indicated that, to the best of their knowledge and experience, criteria for hospitalization of diagnosed malaria cases have been consistent through the years presented in this study. In summary, we selected these study sites because we were informed that no seasonal or secular changes in malaria diagnosis have occurred over the studied periods. In fact, with the exception of Maseno (Fig. 1B), our data did not include missing observations. We also focused on the analysis of cases from all ages to make sound comparisons with previous studies looking at trends, which have been based on a similar set of cases (Hay *et al*. 2000; Shanks *et al*. 2000; Abeku *et al*. 2004; Teklehaimanot *et al*. 2004; Zhou *et al*. 2004; Pascual *et al*. 2008; Pascual and Bouma, 2009; Artzy-Randrup *et al*. 2010; Childs and Boots, 2010; Alonso *et al*. 2011). In the analysis we do not include data for population growth because of the technical difficulties to estimate hospital catchment population, which will be the most desirable denominator to study impacts of population growth on these time series. Although in some instances such growth has been equated to the population growth of the geopolitical subdivisions containing the studied hospitals (Hay *et al*. 2002*a*) in the setting of our study this procedure is unreliable because of changes in geopolitical subdivisions of Kenya containing these hospitals, which increases the likelihood of heterogeneous trends in population growth because of differences in the counted populations (Lewontin and Levins, 1989). Also, this information is not a requisite for non-stationary time series analysis, especially when time series trends are the subject of study (Shumway and Stoffer, 2000).

In our analyses we used rainfall data from Kisumu as a proxy for rainfall in Maseno and Kendu Bay, given the close geographical proximity, <35 km, and similar altitude. DMI is an index for the IOD, defined as the difference in sea surface temperatures (SST) anomalies between western (10°S–10°N, 50°–70°E) and eastern (10°S–0°, 90°–110°E) tropical Indian Ocean (Saji *et al*. 1999). The DMI data were obtained from Japan Agency for Marine-Earth Science and Technology, JAMSTEC,

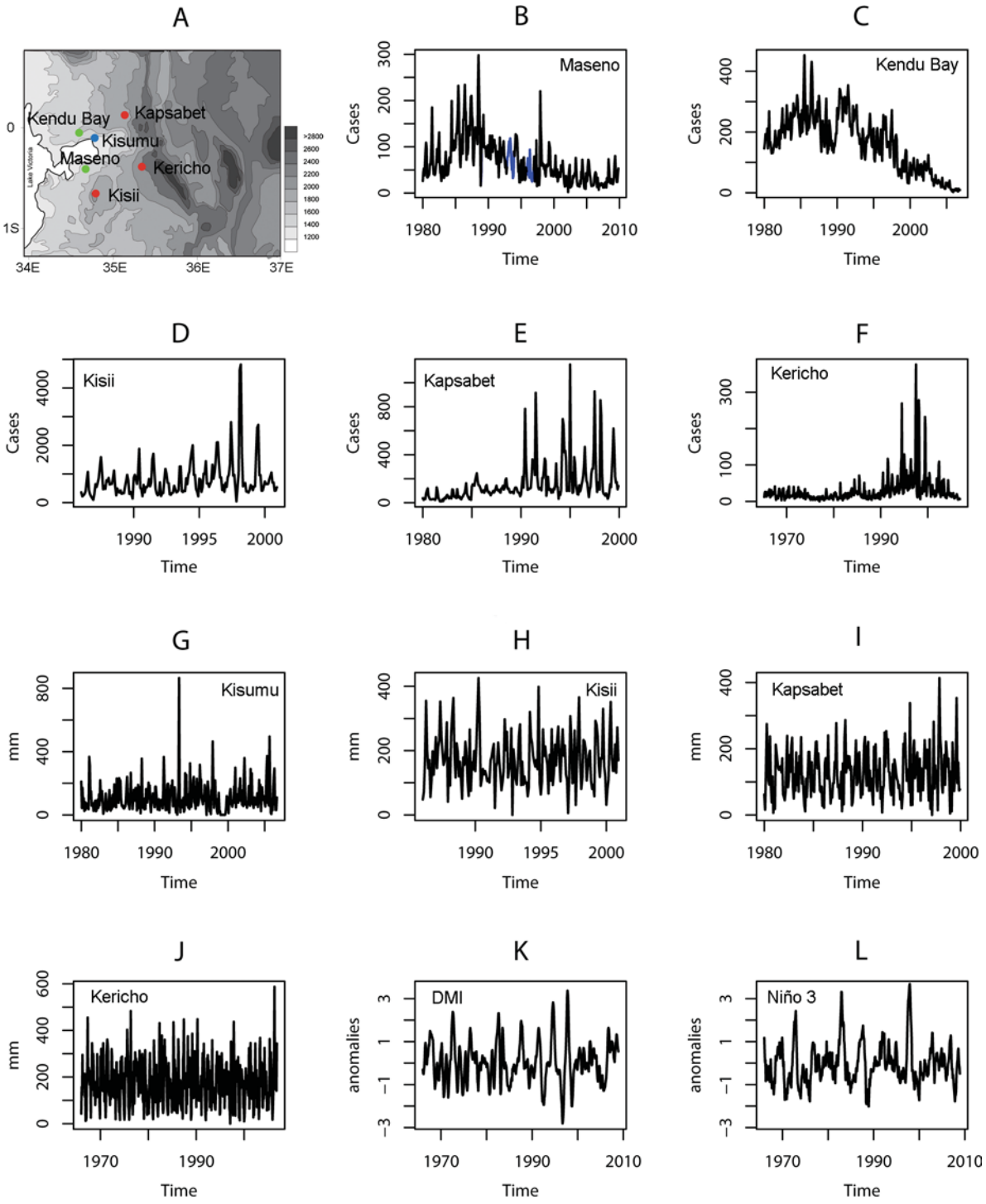

Fig. 1. Data. (A) Hospital locations. Clinical records of malaria infections for: (B) Maseno (May 1935, November 2009, 0°00′15″S, 34°36′16″E, Altitude = 1500 m); (C) Kendu Bay (January 1980, November 2006, 0°24′05″S, 34°39′56″E, Altitude = 1240 m); (D) Kisii (January 1986, December 2000, 0°40′S, 34°46′E, Altitude = 1670 m); (E) Kapsabet (January 1980, December 1999, 0°12′N, 35°06′E, Altitude = 2000 m); (F) Kericho (April 1965, November 2006, 0°23′55″N, 35°15′30″E, Altitude = 2000 m). Rainfall in: (G) Kisumu (January 1980, December 2006, 0°6′S 34°45′E Atltitude = 1131 m); (H) Kisii (January, 1986, December 2000); (I) Kapsabet (January 1980, December 2000); (J) Kericho (January 1966, December 2006). (K) Dipole mode index (January 1966, December 2008) and (L) Niño 3 index (January 1966, December 2008). In panel (A), elevation is measured in meters, m, and indicated by grey. Location color indicates the data available at each site; blue (rainfall); green (disease) and red (disease and rainfall). In panel (B) Blue indicates inputed values (see methods for details).

(www.jamstec.go.jp/frcgc/research/d1/iod/). The strength of the El Niño Southern Oscillation (ENSO) was measured by SST anomalies in El Niño 3 area (150°–90°W, 5°S–5°N) of the Pacific Ocean, using data from the United States National Oceanic and Atmospheric Administration (NOAA)

Climate Prediction Center (www.cpc.ncep.noaa.gov).

Time series analysis for breakpoints and regime shifts in the time domain

Exploratory analysis. To explore the dynamics of the time series, we performed an exploratory time series analysis, by examining the autocorrelation function of the malaria inpatient time series (Shumway and Stoffer, 2000). This inspection showed that most malaria time series (y_t) were first order seasonal autoregressive processes where observations are correlated at both short (1 month) and seasonal time lags (12 months). Thus, we fitted the data to the following seasonal autoregressive null model:

$$y_t = \mu + \phi_1(y_{t-1} - \mu) + \phi_{12}(y_{t-12} - \mu) + \phi_1\phi_{12}(y_{t-13} - \mu) + \alpha\text{Trend} + \varepsilon_t \quad (1)$$

For Kisii and Kericho, the time series were better described by a second order autoregressive process:

$$y_t = \mu + \phi_1(y_{t-1} - \mu) + \phi_2(y_{t-2} - \mu) + \alpha\text{Trend} + \varepsilon_t \quad (2)$$

In models (1) and (2) μ is the average value of the time series, Trend, a non-linear trend estimated with Loess, is included to account for the non-stationarity in the data which, in this case, is the changing mean through time (Chaves and Pascual, 2006). Loess is a non-parametric regression method based on the local fit of polynomials to data which get linked to obtain a smooth function which captures non-linear trends in time series data (Shumway and Stoffer, 2000). The error was assumed to be independent and normally distributed: $\varepsilon \sim N(0,\sigma^2)$. We used models (1) and (2) to pre-whiten the time series of the following climatic covariates: Rainfall, ENSO, and DMI. Pre-whitening is a process that rules out spurious correlation between two time series, by removing (filtering) any common structure between the two studied time series (Chaves and Pascual, 2006). Residuals of the model presented in (1) and the pre-whitened residuals of the climatic covariates were used to compute cross-correlation functions of the number of inpatients with each one of the climatic covariates.

Breakpoints and regime shifts. Data in Fig. 1 suggest the occurrence of secular changes in malaria incidence for the studied period. To test the significance of those apparent changes, and to determine the exact temporal localization of the changes (i.e., breakpoint, the time of an abrupt change indicating a regime shift) we used generalized fluctuation tests for the malaria incidence time series. This technique fits a parametric model to the data and derives an empirical fluctuation process (EFP). Briefly, an empirical fluctuation process depicts residual fluctuation from the studied data. This information can be used to detect unusual changes in, the variability or mean dynamics of, a time series by comparing the unexplained variability of the time series with the fluctuation of a Gaussian random process (Ploberger *et al*. 1989). We estimated EFPs that captured changes in the parameter estimates, where structural changes (i.e., regime shifts) in the time series under study can be observed in time (Ploberger *et al*. 1989; Chaves *et al*. 2008). We estimated the EFP using models that were selected in the absence of breakpoints. We also estimated an EFP for each rainfall time series to investigate possible impacts of regime shifts in covariates as cause of regime shifts in the malaria time series. We did not estimate EFPs for DMI and ENSO since it is well known that most of their variability is interannual (Saji *et al*. 1999; Saji and Yamagata, 2003).

Models to illustrate incidence changes associated with regime shifts. Based on the cross-correlation functions we built models with covariates at lags that had significant cross-correlations and considered the trends obtained with Loess. For the time series in which regime shifts were identified, we further estimated split trends by using the Loess method on the time series split at their breakpoints. We also fitted the best models that we obtained to the split series around the breakpoint. We studied changes on the magnitude of the climatic forcing by the covariates on the malaria time series by comparing the regression coefficients for the model fitted to the different segments of the split time series (Chaves *et al*. 2008). We selected the models using the Akaike Information Criterion (AIC), a metric that selects models based on the number of parameters and likelihood in order to avoid over-parameterized models (Shumway and Stoffer, 2000). Finally, in all cases, assumptions about model error were verified using standard procedures for time series analysis (Shumway and Stoffer, 2000).

RESULTS

All the time series that we studied had a marked seasonality, and their autocorrelation profiles correspond to those of seasonal autoregressive processes (Fig. 2A, E, I, M and Q). Also all the time series were significantly led (having significant cross-correlation at a positive lag) by rainfall (Fig. 2B, F, J, N and Q). With the exception of Maseno (Fig. 2C) and Kapsabet (Fig. 2O), all time series were significantly led by DMI, dipole mode index (Fig. 2G, K, S). ENSO (El Niño 3) significantly led the malaria time series of Kisii (Fig. 2H) and Kericho (Fig. 2 T), but was uncorrelated with malaria dynamics at the other 3 locations (Fig. 2D, 2L, 2P). The regime shift analysis showed that the malaria time series for Maseno (Fig. 3A), Kisii (Fig. 3C) and Kericho (Fig. 3E) had breakpoints. In contrast Kendu Bay (Fig. 3B) and

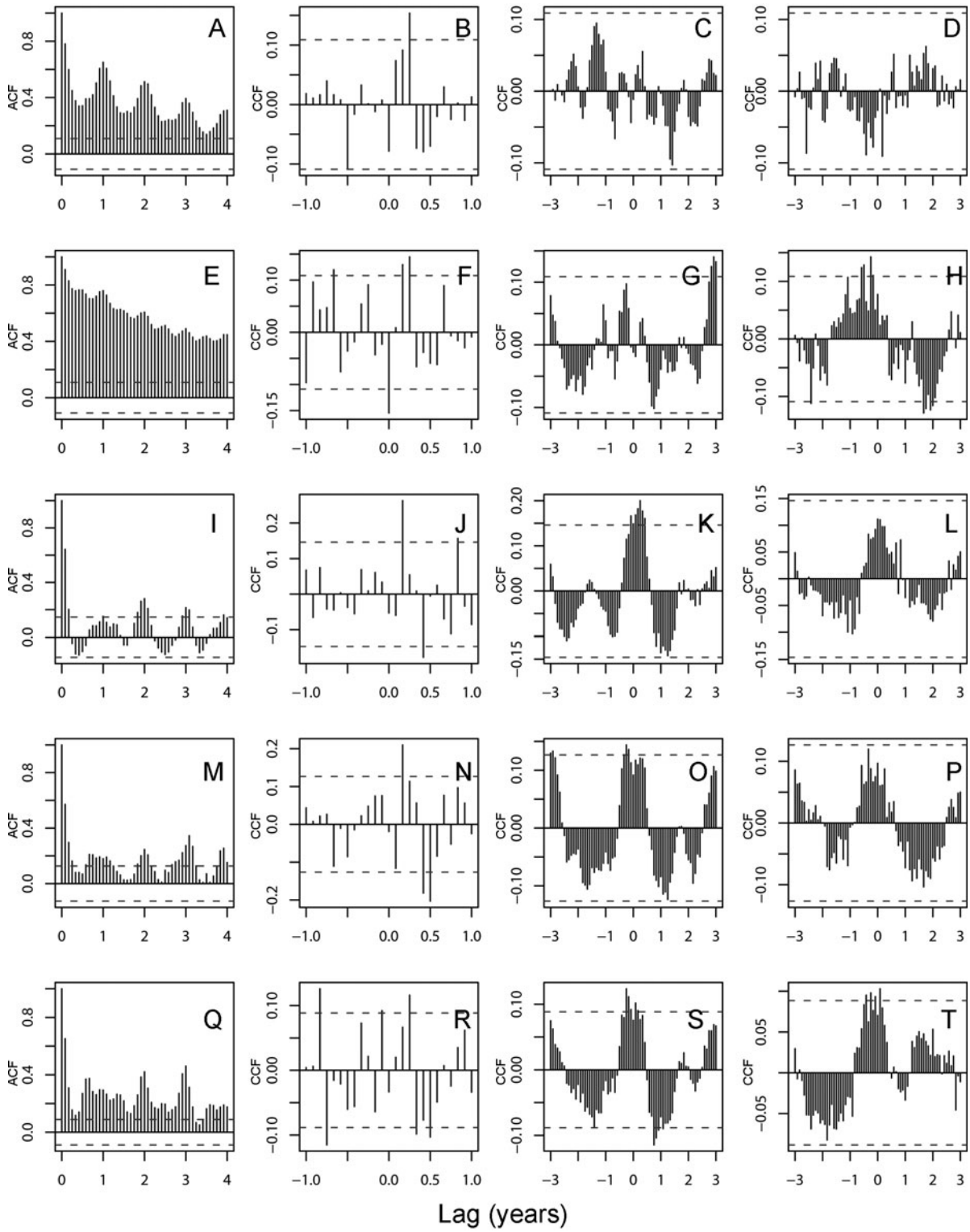

Fig. 2. Autocorrelation (ACF) and cross-correlation functions (CCF) (A) Maseno malaria ACF; (B) Maseno malaria and Kisumu rainfall CCF; (C) Maseno malaria and Dipole mode index, DMI, CCF; (D) Maseno malaria and the Niño 3 index, ENSO; (E) Kendu Bay malaria ACF; (F) Kendu Bay malaria and Kisumu rainfall CCF; (G) Kendu Bay malaria and DMI CCF; (H) Kendu Bay and ENSO CCF; (I) Kisii malaria ACF; (J) Kisii malaria and rainfall CCF; (K) Kisii malaria and DMI CCF; (L) Kisii malaria and ENSO CCC; (M) Kapsabet malaria ACF; (N) Kapsabet and rainfall CCF; (O) Kapsabet malaria and DMI CCF; (P) Kapsabet malaria and ENSO CCF; (Q) Kericho malaria ACF; (R) Kericho malaria and rainfall CCF; (S) Kericho malaria and DMI CCF; (T) Kericho malaria and ENSO CCF. In the x axis of all plots lag = 1 means 12 months, dashed lines indicate the 95% confidence limits within which the ACFs and CCFs are not different from what is expected by random.

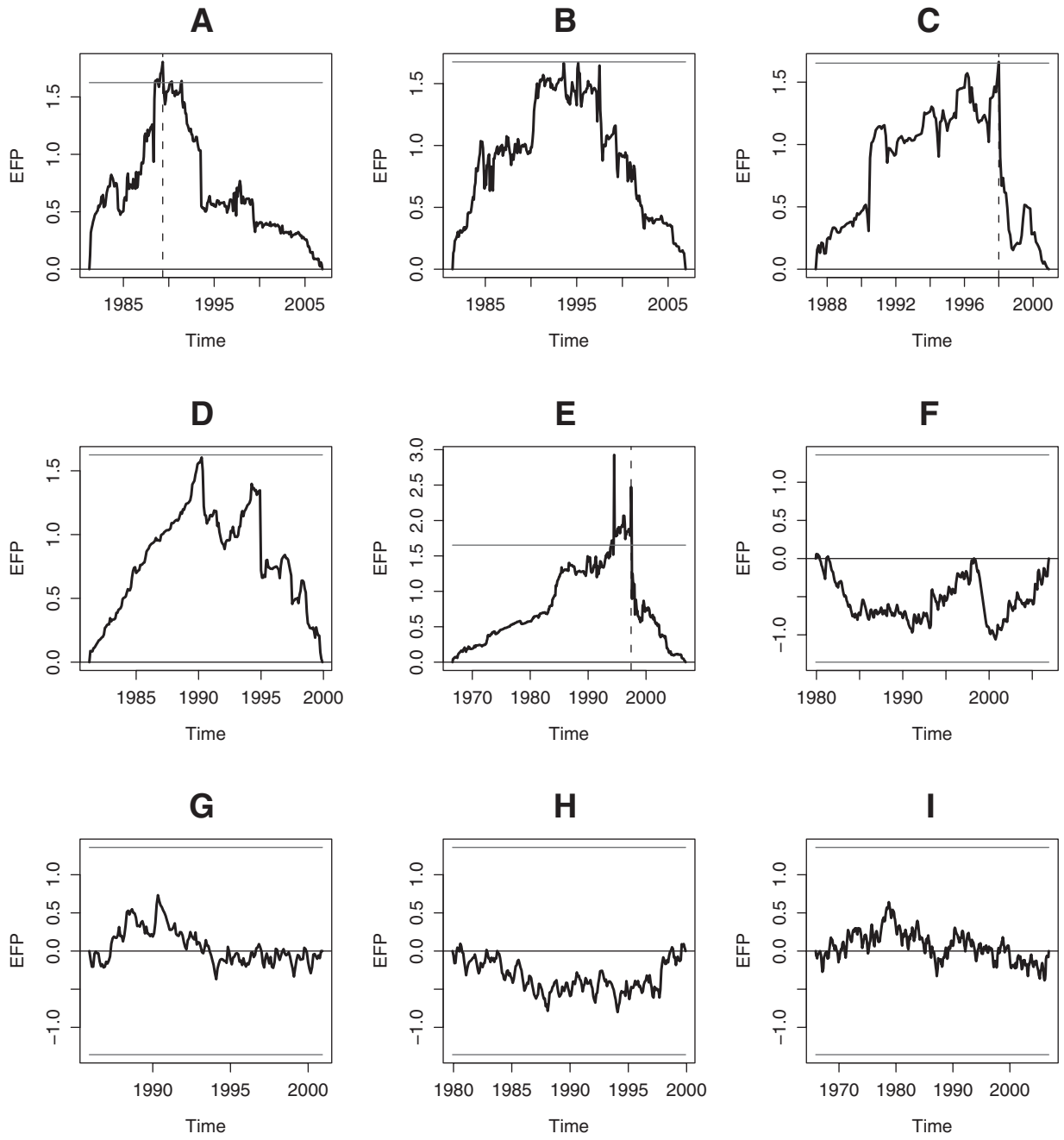

Fig. 3. Breakpoints for malaria incidence and rainfall time series. (A) Empirical fluctuation process, EFP, for Maseno malaria time series, as a seasonal autoregressive process with a non-linear trend, the dashed line indicates the most likely breakpoint, May 1989 (RE = 1·80, $P < 0·01$); (B) EFP for Kendu Bay malaria time series as a seasonal autoregressive process with a non-linear trend, no indications of breakpoints (RE = 1·67, $P > 0·05$); (C) EFP for Kisii as a first order seasonal second order autoregressive process with a non-linear trend, the dashed line indicates the most likely breakpoint, January 1998 (RE = 1·66, $P < 0·047$); (D) EFP for Kapsabet, as a seasonal autoregressive process with a non-linear trend, no indications of breakpoints, (RE = 1·60, $P > 0·05$); (E) EFP for Kericho as a first order seasonal second-order autoregressive process with a non-linear trend, the dashed line indicates the most likely breakpoint, June 1997(RE = 2·93, $P < 10^{-7}$); (F) Empirical fluctuation process, EFP, for Kisumu rainfall (RE = 1·06, $P < 0·21$); (G) EFP Kisii rainfall (RE = 0·73, $P < 0·66$); (H) EFP Kapsabet rainfall (RE = 0·80, $P < 0·54$); (I) EFP Kericho (RE = 0·64, $P < 0·80$). In all panels when values exceed the outer solid lines is an indication of a regime shift. In all panels the outer lines correspond to the extreme values expected if changes in the coefficients are driven by a random walk.

Kapsabet (Fig. 3D) had no breakpoints. None of the rainfall time series showed any breakpoints (Fig. 3F, G, H, I).

Seasonal autoregressive models confirmed the association between malaria incidence and rainfall observed in the cross-correlation analysis (Table 1). Figure 4 shows that for Maseno (Fig. 4A) and Kendu Bay (Fig. 4D) malaria incidence began a decreasing trend in the late 1980s. By contrast, in Kisii (Fig. 4B), Kericho (Fig. 4C) and Kapsabet (Fig. 4D) increasing

Table 1. Model Selection

(Time series indicates the malaria time series, autoregressive components indicate the number of ordinary and seasonal autoregressive components respectively. Covariates indicate the different covariates with the respective lag, in months, within parenthesis: Trend is the non-linear trend obtained using loess, Rainfall, the local rainfall (in Maseno and Kendu Bay, rainfall from Kisumu was used as a proxy); ENSO, the Niño 3 index, and DMI, the dipole mode index. Breakpoint indicates whether a breakpoint was considered (Y) or not (N) and AIC indicates the Akaike Information criterion, highlighted values show the best models (minimum AIC).)

Time Series	Autoregressive components	Autoregressive components (Seasonal)	Covariates	Breakpoint	AIC
Maseno	1	1	Trend	N	3069·2
	1	1	Split Trend	N	3056·6
	1	1	Trend, Rainfall(3)	N	3063·1
	1	1	Split Trend, Rainfall(3)	N	3050·3
	1	1	Trend, Rainfall(3)	Y	3024·4
	1	1	Split Trend, Rainfall(3)	Y	**3018·8**
Kendu Bay	1	1	Trend	N	3226·7
	1	1	Trend, Rainfall(0), Rainfall(3), ENSO(22), DMI(35)	N	3213·0
	1	1	Trend, Rainfall(0), Rainfall(3), DMI(35)	N	**3211·0**
Kisii	2	1	Trend	N	2685
	2	0	Trend	N	2685
	2	0	Split Trend	N	2719·4
	2	0	Trend, Rainfall(2), DMI(2)	N	2668·4
	2	0	Split Trend, Rainfall(2), DMI(2)	N	2674·8
	2	0	Trend, Rainfall(2), DMI(2)	Y	**2613·5**
	2	0	Split Trend, Rainfall(2), DMI(2)	Y	**2613·5**
Kapsabet	1	1	Trend	N	2963·1
	1	0	Trend	N	2961·1
	1	0	Trend, Rainfall(2), Rainfall(6)	N	**2943·7**
Kericho	2	1	Trend	N	4551·1
	2	0	Trend	N	4549·4
	2	0	Split Trend	N	4538·7
	2	0	Trend, Rainfall(3), ENSO(2), DMI(1)	N	4543·2
	2	0	Split Trend, Rainfall(3), ENSO(2), DMI(1)	N	4511·5
	2	0	Trend, Rainfall(3), DMI(1)	N	4542·33
	2	0	Split Trend, Rainfall(3), DMI(1)	N	4509·55
	2	0	Trend, Rainfall(3), DMI(1)	Y	4482·88
	2	0	Split Trend, Rainfall(3), DMI(1)	Y	**4432·4**

trends in malaria transmission were observed in the mid and late 1990s and these trends began to decrease in the early 2000s (Fig. 4B, C and D). In general, split trends showed similar patterns to contiguous trends (Fig. 4A, B, C). However, it is important to note that in Kisii, the second half of the split trend gave too much importance to a few observations (Fig. 4B). In all the best models (Table 1) normality and homokedasticity tests confirmed that the error was normal, independent and identically distributed, thus confirming the validity of our analyses.

Regarding the influence of climatic covariates, with the exception of Kendu Bay and Kapsabet where rainfall had both positive and negative impacts on malaria incidence, rainfall significantly increased monthly malaria incidence (Table 2). The process of model selection showed that for those time series that were associated with both El Niño 3 and DMI, the latter was the best predictor (Table 1). Increases in DMI were positively associated with increases in malaria incidence. In Maseno and Kericho the inclusion of the breakpoints and splits trends maximized the likelihood of the models (Table 1). In Kisii only the inclusion of the breakpoint improved model fit (Table 1), probably because of the irregular second half of the split time series (Fig. 4B). Finally, Maseno and Kericho show opposits patterns regarding the variability associated with their regime shifts. In Maseno, the variability measured model standard deviation ($\hat{\sigma}$, Table 2) decreased after the breakpoint, while in Kisii and Kericho it increased.

DISCUSSION

The possible association between changes in highland malaria transmission patterns and global warming has motivated a heated debate (Chaves and Koenraadt, 2010). From positions that claim to have explained malaria trends as a direct product of temperature trends (Alonso *et al*. 2011) to positions that neglect the known impacts that changing

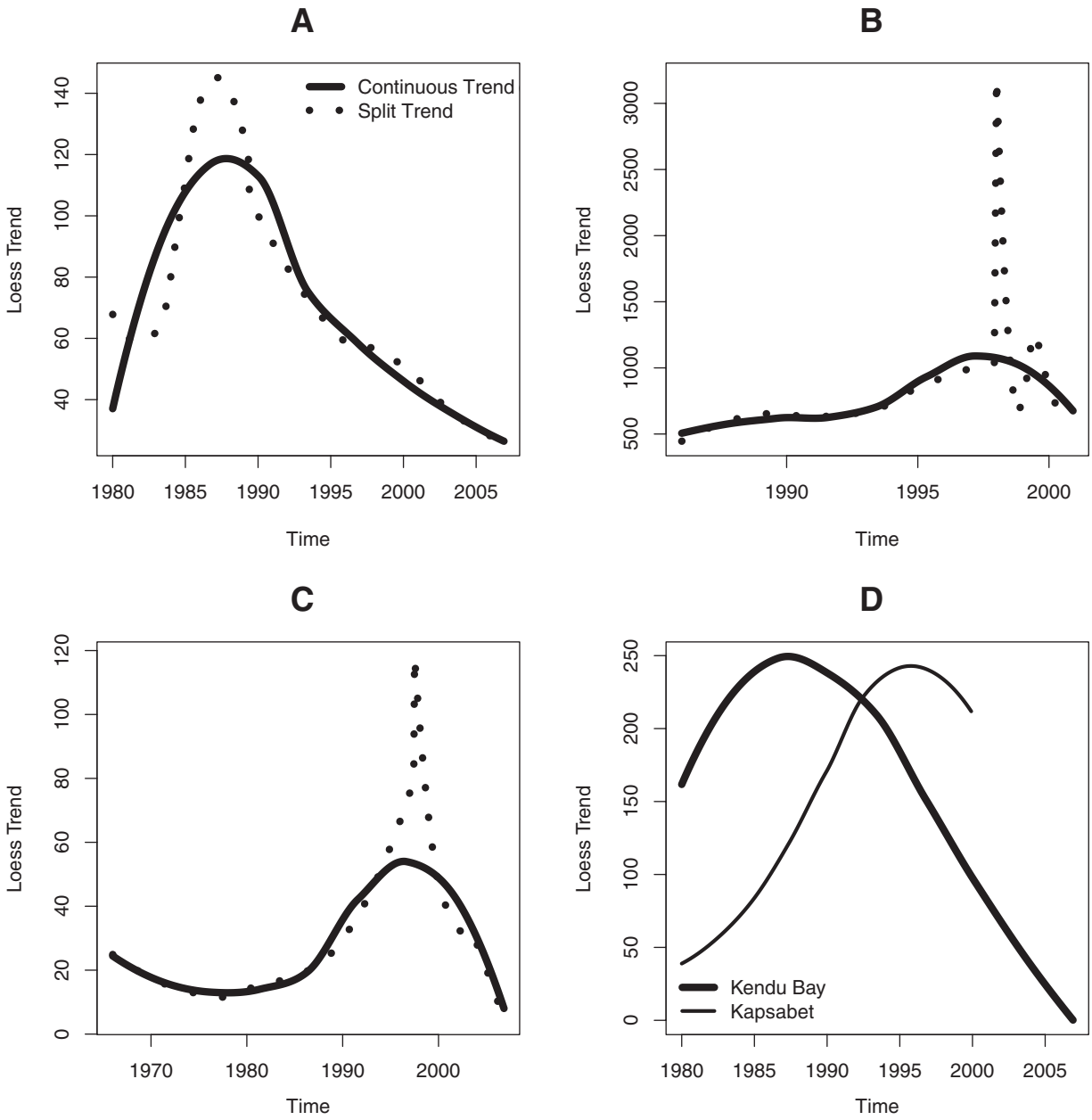

Fig. 4. Malaria trends obtained with Loess. (A) Maseno (B) Kissi (C) Kericho (D) Kendu Bay and Kapsabet. In all panels continuous lines indicate continuous trends. In panels (A), (B) and (C), the dotted lines indicate split trends.

environments have on organisms (Reiter, 2008), efforts to understand the linkages between malaria transmission and climate change have lacked robustness in the validation of inferences with independent observations (Levins, 2006). This is illustrated by the many studies that have exclusively focused on Kericho (Hay *et al*. 2000; Shanks *et al*. 2005; Pascual *et al*. 2008; Artzy-Randrup *et al*. 2010; Childs and Boots, 2010; Alonso *et al*. 2011).

Here, we have taken a different approach and studied 5 time series from Lake Victoria basin, an area with common regional rainfall patterns (Anyah and Semazzi, 2004; Anyah *et al*. 2006) and a homogeneous signature of global climatic phenomena like the IOD (Saji *et al*. 1999; Saji and Yamagata, 2003). With the 5 time series we attempted to characterize patterns of malaria incidence. However, extending the analysis to 5 sites had the cost of uncertainty about homogeneity in data quality, especially when compared with Kericho, which is assumed to have less uncertainty in the parasitological confirmation of cases (Hay *et al*. 2000, 2002*a*; Shanks *et al*. 2000, 2002, 2005). Nevertheless, we consider the data are comparable because of their common attributes: (i) all time series only consider the most severe (or virulent in a wider biological sense) malaria cases, those requiring admission to the hospital (inpatient data); (ii) in all cases the first line of diagnosis was merely clinical (passive detection); (iii) malaria is the most likely disease to produce morbidity with severe malaria symptoms in the area (Menge *et al*. 2008; Feikin *et al*. 2010); (iv) there were

Table 2. Parameter estimates

(Time series indicates the malaria time series. Parameter indicates the predictor for which the parameter was estimated: Mean is the mean value of the series, AR and SAR are, respectively, ordinary and seasonal autoregressive predictors, Trend is the non-linear trend obtained with loess, Rainfall is the local rainfall (Kisumu rainfall for Maseno and Kendu Bay). The value inside the parenthesis indicates the lag of the covariates (in months). No shift presents estimates for models without breakpoints. Before and After present, respectively, estimates before and after the breakpoints. P (<0·05) indicates the significance of each parameter in the models N (no shift)/ B (before breakpoint)/ A (after breakpoint).)

Time Series	Parameter (Lag)		No Shift	Before	After	P (<0·05)
Maseno	$\hat{\mu}$	Mean(-)	71·95 ± 3·97	74·80 ± 11·43	72·14 ± 4·06	N/B/A
	ϕ_1	AR(1)	0·51 ± 0·05	0·53 ± 0·09	0·44 ± 0·06	N/B/A
	ϕ_{12}	SAR(12)	0·27 ± 0·05	0·36 ± 0·11	0·25 ± 0·06	N/B/A
	$\hat{\alpha}$	Split Trend(-)	1·03 ± 0·11	0·99 ± 0·25	1·03 ± 0·15	N/B/A
	$\hat{\beta}$	Rainfall(3)	0·046 ± 0·016	0·13 ± 0·04	0·019 ± 0·015	N/B
	$\hat{\sigma}$	—	26·25	31·41	21·43	—
Kendu Bay	$\hat{\mu}$	Mean(-)	167·75 ± 6·83	—	—	N
	ϕ_1	AR(1)	0·64 ± 0·04	—	—	N
	ϕ_{12}	SAR(12)	0·21 ± 0·06	—	—	N
	$\hat{\alpha}$	Trend(-)	1·02 ± 0·08	—	—	N
	$\hat{\beta}_1$	Rainfall(0)	−0·048 ± 0·020	—	—	N
	$\hat{\beta}_2$	Rainfall(3)	0·045 ± 0·020	—	—	N
	$\hat{\gamma}$	DMI(35)	11·51 ± 3·95	—	—	N
	$\hat{\sigma}$	—	33·45	—	—	—
Kisii*	$\hat{\mu}$	Mean(-)	787·19 ± 53·64	763·37 ± 57·39	569·57 ± 210·13	N/B/A
	ϕ_1	AR(1)	0·77 ± 0·07	0·60 ± 0·10	0·82 ± 0·16	N/B/A
	ϕ_{12}	AR(2)	−0·36 ± 0·07	−0·06 ± 0·10	−0·47 ± 0·19	N/A
	$\hat{\alpha}$	Trend(-)	1·16 ± 0·28	0·86 ± 0·30	3·28 ± 1·14	N/B/A
	$\hat{\beta}$	Rainfall(2)	1·47 ± 0·37	1·69 ± 0·37	0·79 ± 1·20	N/B
	$\hat{\gamma}$	DMI(2)	117·17 ± 47·88	8·08 ± 44·82	657·33 ± 159·19	N/A
	$\hat{\sigma}$	—	417·95	313·29	502·6	—
Kapsabet	$\hat{\mu}$	Mean(-)	158·86 ± 26·18	—	—	N
	ϕ_1	AR(1)	0·43 ± 0·06	—	—	N
	$\hat{\alpha}$	Trend(-)	0·99 ± 0·20	—	—	N
	$\hat{\beta}_1$	Rainfall(2)	0·38 ± 0·12	—	—	N
	$\hat{\beta}_2$	Rainfall(6)	−0·40 ± 0·12	—	—	N
	$\hat{\sigma}$	—	127·10	—	—	—
Kericho	$\hat{\mu}$	Mean(-)	28·63 ± 1·66	31·70 ± 2·49	29·68 ± 5·13	N/B/A
	ϕ_1	AR(1)	0·66 ± 0·04	0·67 ± 0·06	0·85 ± 0·08	N/B/A
	ϕ_2	AR(2)	−0·32 ± 0·04	−0·10 ± 0·07	−0·46 ± 0·09	N /A
	$\hat{\alpha}$	Split Trend(-)	1·01 ± 0·08	1·47 ± 0·16	0·71 ± 0·19	N/B/A
	$\hat{\beta}$	Rainfall (3)	0·026 ± 0·012	0·025 ± 0·012	0·024 ± 0·028	N/B
	$\hat{\gamma}$	DMI(1)	3·26 ± 1·76	5·77 ± 2·25	4·20 ± 5·55	B
	$\hat{\sigma}$	—	24·20	20·12	29·86	—

* These are the parameters for the model with a contiguous trend (see Table 1 and Results).

no systematic changes in the implementation of malaria confirmation i.e., we have no reason to suspect any seasonal, or secular, change in diagnostic criteria at each site. Obviously, these biases on the data limits the inferences to severe cases, which most likely underestimate disease transmission as shown by highly standardized blood-slide examination (Molineaux *et al*. 1980) and molecular diagnostic techniques (Ofulla *et al*. 2005; Menge *et al*. 2008), not to mention the likelihood of inaccuracy that could emerge from stressed staff dealing with epidemics at resource limited health facilities. However, since the type of cases studied over time were homogeneous, there is no threat to comparison validity over time, because the data fits the standards for a sound analysis of trends (Shumway and Stoffer, 2000).

Our results show that malaria incidence in Lake Victoria basin displayed trends that are similar over given altitudinal ranges. At altitudes below 1600 m, we found that malaria trends began to decrease in the late 1980s. In contrast, at higher altitudes, above 1600 m, we found that malaria increased in the mid and late 1990s, confirming a pattern noticed in East Africa that linked unexpectedly high levels of malaria transmission associated with IOD and ENSO (Hashizume *et al*. 2009; Lindblade *et al*. 1999, 2001; Zhou *et al*. 2004). In this context, population growth is indirectly associated with malaria emergence in the African highlands because of its impact on land use change, and subsequent changes in the ecology of living organisms involved in malaria transmission (Lindblade *et al*. 2000). Montane

rainforests used to cover the highlands surrounding Lake Victoria, while the lowlands in the lake basin were less forested. Now the highland forests have mostly disappeared, and locals are still clearing the last patches of forest that remained in the valley bottoms (Verschuren *et al*. 2002), mainly for the purposes of self-subsistence agriculture (Ernst *et al*. 2009). In addition, population growth in this region, with a long history of unequal access to land derived from colonial plundering (Prothero, 1965; Chaves and Koenraadt, 2010), also forces locals to migrate to valley bottoms where they are likely exposed to a large number of vectors and high malaria transmission (Munyekenye *et al*. 2005). Thus, the indirect impacts of population growth, which are ultimately expressed in diverse degrees of land transformation and human movement, make our analysis robust to the lack of explicit consideration of population growth data. Moreover, regulation of malaria transmission, which is best described by frequency dependent models (Hay *et al*. 2000; Pascual *et al*. 2008; Chaves *et al*. 2009; Alonso *et al*. 2011), implies that population growth plays a relatively minor role on the dynamics of transmission (McCallum *et al*. 2001). In fact, several studies have shown that there is not a direct mapping between population growth and trends in malaria transmission, both in this area (Hay *et al*. 2002*a*,*b*; Pascual *et al*. 2008; Alonso *et al*. 2011) and outside Africa (Chaves *et al*. 2009). On the other hand, frequency dependent transmission models are sensitive to conditions of population immunity, which is indeed reduced in highland populations, when compared to lowland populations (John *et al*. 2002), as product of a decreased exposure to malaria infection (Drakeley *et al*. 2005).

The late 1990s malaria epidemics in lake Victoria basin, above 1600 m, were so large that they significantly increased the variance of the time series; probably explaining the occurrence of breakpoints in Kisii and Kericho in 1997/1998. One hypothesis that could explain the synchrony in the breakpoints, which requires further testing in the field, is the synchronization of mosquito populations and subsequent malaria transmission triggered by rainfall. Previous studies have shown that catching adult *Anopheles gambiae* mosquitoes, the main malaria vector in East Africa highlands, is extremely difficult (Koenraadt *et al*. 2006). Even so, vector densities have been shown to significantly increase following rainfall (Minakawa *et al*. 2002, 2005*b*, 2006), even if prolonged rainfall can wash away mosquito larvae (Paaijmans *et al*. 2007). Occasional floods and rainfall runoff create numerous stagnant water pools in valley bottoms that are poorly drained. If riparian forests are cleared, these stagnant water pools become suitable breeding sites for major malaria vectors that mainly inhabit small sun-lit water pools, *An. gambiae and An. arabiensis* (Gimnig *et al*. 2001; Minakawa *et al*. 2005*a*). Besides its direct impact on mosquito density, rainfall also determines a series of wetness indices that are major risk factors for malaria infection in western Kenya (Cohen *et al*. 2010), probably by enhancing mosquito movement across the landscape, a pattern common among several mosquito genera, including *Anopheles* (Silver, 2008). Thus, to explain the heterogeneity in malaria transmission trends, we consider that finely grained landscape transformation, in synergy with increased rainfall associated with IOD (Hashizume *et al*. 2009), probably were major drivers of the large epidemics above 1600 m.

Regarding the decreasing malaria trends, the mechanism driving changes at low and high altitudes seems to be different. At low altitude, below 1600 m, malaria trends began to decrease before the 1990s, and could likely reflect self-regulation of transmission, either by immunity development (Hay *et al*. 2000; Pascual *et al*. 2008), or the more general reduced inflow of susceptible individuals, i.e., immune adults and well protected children, as observed outside Africa (Chaves *et al*. 2008, 2009, 2011; Kaneko *et al*. 1998, 2000). At high altitude (>1600 m), large-scale malaria control interventions with insecticide treated bednets could have driven both the reduction of malaria transmission and mosquito population size (Lindblade *et al*. 2004) and a shift of dominant vector species, from *An. gambiae* to *An. arabiensis* (Bayoh *et al*. 2010). In fact, the interruption of malaria transmission has been documented in highland sites near the locations we studied (John *et al*. 2009; Zhou *et al*. 2011). More, generally differences in malaria incidence trends can reflect a myriad of historic changes in East Africa. From demographic changes to land use changes (Lindblade *et al*. 2000; Lindsay and Martens, 1998), drug resistance (Shanks *et al*. 2005), and global warming (Alonso *et al*. 2011) differences in malaria trends ultimately link the sensitivity of malaria transmission to its context (Chaves and Koenraadt, 2010). Finally, the scarcity of contextual information and long-term malaria records necessary to robustly determine the drivers behind malaria transmission trends highlight the need for surveillance and for climatic and demographic systems able to record high quality data. These data are necessary to understand heterogeneities in malaria transmission across spatial scales and to make sound inferences about the impacts of climate change and control/elimination interventions on malaria transmission.

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