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Association between climate variability and malaria epidemics in the East African highlands

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The causes of the recent reemergence of *Plasmodium falciparum* epidemic malaria in the East African highlands are controversial. Regional climate changes have been invoked as a major factor; however, assessing the impact of climate in malaria resurgence is difficult due to high spatial and temporal climate variability and the lack of long-term data series on malaria cases from different sites. Climate variability, defined as short-term fluctuations around the mean climate state, may be epidemiologically more relevant than mean temperature change, but its effects on malaria epidemics have not been rigorously examined. Here we used nonlinear mixed-regression model to investigate the association between autoregression (number of malaria outpatients during the previous time period), seasonality and climate variability, and the number of monthly malaria outpatients of the past 10–20 years in seven highland sites in East Africa. The model explained 65–81% of the variance in the number of monthly malaria outpatients. Nonlinear and synergistic effects of temperature and rainfall on the number of malaria outpatients were found in all seven sites. The net variance in the number of monthly malaria outpatients caused by autoregression and seasonality varied among sites and ranged from 18 to 63% (mean = 38.6%), whereas 12–63% (mean = 36.1%) of variance is attributed to climate variability. Our results suggest that there was a high spatial variation in the sensitivity of malaria outpatient number to climate fluctuations in the highlands, and that climate variability played an important role in initiating malaria epidemics in the East African highlands.

climate change | statistical modeling | *Plasmodium falciparum* | time series analysis

Malaria is a major public health problem in sub-Saharan Africa (1). The high-elevation areas in East Africa had infrequent epidemic malaria between the 1920s and the 1950s (2, 3). Malaria epidemics were not reported between the 1960s and the early 1980s after a malaria eradication campaign (4, 5). Although the lack of documented epidemics in the highlands between the 1960s and the early 1980s could have been due to the methods for health data recording at the health clinics, it is well recognized that a series of malaria epidemics have occurred in the East African highlands, including the highlands in western Kenya (6–13), Uganda (11), Ethiopia, Tanzania (14, 15), Rwanda (8), and Madagascar (6, 11). As a consequence of low immunity in the human population of the highlands, malaria epidemics have caused significant human mortality in both children (13) and adults (16). Compared to the malaria situation between the 1920s and 1950s, the current pattern of malaria in the highlands is characterized by increased frequencies (17), expanded geographic areas (18), and increased case-fatality rates (19).

The causes of the recent reemergence of *Plasmodium falciparum* epidemic malaria in the East African highlands are controversial. Several mechanisms have been hypothesized, including (*i*) increased travel from the malaria-endemic Lake Victoria basin to the highlands (20–22); (*ii*) degradation of the healthcare infrastructure (9–11); (*iii*) antimalarial drug resistance (22–24); (*iv*) local malaria transmission in the highlands as a consequence of land-use changes (9, 11, 25); and (*v*) global warming (8, 26, 27). Malakooti *et al.* (10) analyzed the hospital clinical records and questionnaire survey results in a highland tea plantation estate in Kericho (≈1,700 m above sea level), western Kenya, and concluded that the increased travel and healthcare infrastructure degradation should not be the key factors for the reemergence of highland malaria. Their conclusions are supported by the facts that the majority (92%) of malaria patients did not travel to malaria-endemic areas, and that the healthcare system in their study area has not been degraded. Drug resistance can only aggravate malaria-induced morbidity and mortality; it cannot initiate an epidemic. In addition, drug resistance could not explain the sporadic malaria epidemics in the Kenyan highlands in the 1920s to 1950s, when the problem of drug resistance was insignificant (18). The reemergence of epidemic malaria is likely due to local malaria transmission in the highlands (10).

The role of climate as a driving force for malaria epidemics in the highlands is a subject of considerable discussion (22). Despite an increase in the global average surface temperature during the past century by 0.6 ± 0.2°C (28), Hay *et al.* (29) concluded that mean temperature and rainfall have not changed significantly in the past century at four locations in the East African highlands, where malaria incidence has been increasing. However, their use of spatially interpolated climate data were criticized for its inappropriateness for trend analysis in areas known to have a high spatial heterogeneity in temperature (30). Assessing the impact of climate in malaria resurgence is difficult because of high spatial climate variability and the lack of a long-term data series on malaria cases from different sites. Temperature affects the development rates and survivorship of malaria parasites and mosquito vectors. Rainfall influences the availability of mosquito larval habitats and thus mosquito demography. Temperature and rainfall may have synergistic effects on malaria transmission. Thus, simultaneous analysis on the long-term time series of meteorological and parasitological data are critically needed to demonstrate the effects of climate on malaria cases. Moreover, climate variability (short-term fluctuations around the mean climate state on a fine time scale) may be epidemiologically more relevant than the mean temperature increase (31). However, the association between climate variability and malaria epidemics has not been rigorously examined.

In this study, we used nonlinear time series analysis to investigate the association between climatic variability and the number of monthly malaria outpatients over the past 10–20 years in seven highland sites in East Africa where malaria epidemics have been reported. We are particularly interested in the synergistic effects of temperature and rainfall on the number of malaria outpatients and spatial variation in the sensitivity of malaria outpatient numbers to climate conditions. This knowledge is critical to the development of malaria early warning systems for the East African highlands.

Materials and Methods

Climate and Malaria Outpatient Data Collection. We investigated the association between climatic variability and number of malaria

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Table 1. Descriptions of the study sites and malaria outpatient time series data source

Country	Site (geographic coordinates and elevation)	Malaria outpatient data period	Long-term mean climate (1978–1998)			Malaria outpatient time series data source
			Maximum monthly temperature, °C	Minimum monthly temperature, °C	Annual rainfall, mm	
Ethiopia	Alaba (7.30°N, 38.17°E, 1,500–2,100 m)	1988–1999	26.8	12.9	646	Ref. 52
	Ziway (7.81°N, 38.63°E, 1,500–2,300 m)	1991–1999	26.2	12.7	598	Ref. 52
Kenya	Kericho (0.30°S, 35.25°E, 1,500–2,300 m)	1978–1998	23.2	11.0	1,814	Ref. 17
	Kilgoris (1.07°S, 34.96°E, 1,400–2,100 m)	1980–1999	25.2	15.5	1,936	Ref. 13
	Eldoret (0.46°N, 35.23°E, 1,800–2,200 m)	1985–1998	23.3	10.8	982	Refs. 12 and 53
	Nandi (0.22°N, 35.10°E, 1,800–2,200 m)	1980–1999	25.8	13.4	1,463	This study
Uganda	Kabala (1.27°S, 30.04°E, 1,650–2,300 m)	1992–1998	23.2	12.3	1,196	Refs. 11 and 53

outpatients in seven highland sites in Ethiopia, Kenya, and Uganda. Detailed information on the locations of the study sites, climatic conditions, and sources of monthly malaria outpatient number is presented in Table 1. The Kilgoris site included malaria patients <15 years of age (32), whereas malaria outpatients of all ages were included in other sites. The period that malaria outpatient data were available varies from 10 to 20 years among the seven sites (Table 1). The meteorological data from 1978 to 1998 were actual weather station records, downloaded from the African Remote Sensing Data Bank (http://informatics.icipe.org/databank) and the Surface Data of the World Meteorological Organization (www.ncdc.noaa.gov/oa/climate/climatedata.html), including daily maximum and minimum temperature and daily rainfall at each of the seven sites. Meteorological data of Kilgoris were based on the weather station data in Kisii of similar elevation, ≈35 km from Kilgoris. The maximum and minimum monthly temperature and monthly rainfall were calculated from the daily records and used for all analyses. Malaria vector population dynamics were not examined because the corresponding long-term data on trends in *Anopheles* vector populations are not available for the study sites.

Statistical Analysis. ***Climate changes and frequency of malaria epidemics.*** We are particularly interested in whether climate warming has occurred and climate variability was higher in 1989–1998 than in 1978–1988 because frequent malaria outbreaks have occurred in the East African highlands since 1989. For each of the seven study sites, we compared average maximum monthly temperature, minimum monthly temperature, and rainfall over the periods of 1978–1988 and 1989–1998 by using the *t* test. Climate variability is measured by the annual variance of the three meteorological variables (maximum temperature, minimum temperature, and rainfall). Changes in monthly minimum and maximum temperature and rainfall at each site were expressed as standardized anomalies relative to the 1961–1990 mean for each site. The 1961–1990 mean was obtained from the almanac characterization tool (ACT) for each site (33). The standardized anomaly is calculated as the difference between time series data and the mean values divided by the standard deviation. Annual variance in the maximum and minimum monthly temperature and rainfall in any given year was calculated from the 12-month mean. The difference in the mean annual variance of the three meteorological variables between 1978–1988 and 1989–1998 was tested by using the *t* test, assuming different variances for each period.

Epidemic detection was based on the method proposed by Cullen *et al.* (34). The epidemic alert threshold for each month was determined as the average monthly malaria cases in the past 5 years plus two times the standard deviation. Malaria case data were not transformed. Hay *et al.* (13) compared three malaria epidemic detection methods and showed that Cullen's method based on untransformed monthly malaria outpatient numbers is a sensitive method. The proportion of the total number of epidemic months between 1978–1988 and 1989–1998 was calculated.

Statistical association between climate variability and malaria incidence. The number of malaria outpatients, N_t, at a given time is likely to be affected by the previous number of malaria outpatients (autoregression), seasonality, and climate variability. Thus, the dynamics of the number of monthly malaria outpatients can be modeled as

$$N_t = f(N_{i<t}, t) + g(T_{\min}(t), T_{\max}(t), R_{\text{ain}}(t)) + e_t, \qquad [1]$$

where

$$f(N_{i<t}, t) = \alpha + \sum_{i=1}^{d} \beta_i N_{t-i} + b_1 \cos\left(\frac{2\pi}{12} t\right) + b_2 \sin\left(\frac{2\pi}{12} t\right) \qquad [2]$$

$$g = r_1 \sum_{i=\tau_1}^{\tau_{\min}} T_{\min}(i) + r_2 \sum_{i=\tau_2}^{\tau_{\max}} T_{\max} + r_3 \sum_{i=\tau_3}^{\tau_R} R_{\text{ain}}(i) + r_4 \sum_{i=\tau_1}^{\tau_{\min}} T_{\min}(i) \times \sum_{i=\tau_3}^{\tau_R} R_{\text{ain}}(i) + r_5 \sum_{i=\tau_2}^{\tau_{\max}} T_{\max}(i) \times \sum_{i=\tau_3}^{\tau_R} R_{\text{ain}}(i). \qquad [3]$$

The term $f(N_{i<t}, t)$ is a higher-order autoregressive model that tests the effect of autoregression, $g(T_{\min}(t), T_{\max}(t), R_{\text{ain}}(t))$ represents the effects of climate variability on malaria incidence, and e_t represents random noise. N_t was not adjusted for annual human population growth rates because the number of hospitals generally increases in proportion to human population size increase, and thus the human population size that each hospital has served remains similar during the study period (35). Parameter α is the deterministic drift, and β_i measures the lagged effect (autoregression). *d,* the maximum number of lagged months, is determined by the lagged autoregression analysis between monthly malaria incidences (36). Seasonality in the number of malaria outpatients was implemented by the sin and cos functions (37). r_i is the regression coefficient, $T_{\min}$ and $T_{\max}$ represent minimum and maximum monthly temperature, and R_{ain} represents monthly rainfall. The terms (τ_1, $\tau_{\min}$), (τ_2, $\tau_{\max}$), and (τ_3, τ_R) represent the time lag periods when minimum and maximum monthly temperature and rainfall exhibited significant lagged correlation with the number of malaria outpatients as determined by the significance tests of cross-correlation function. Thus, $\sum_{i=\tau_1}^{\tau_{min}} T_{\min}(i)$ and $\sum_{i=\tau_2}^{\tau_{max}} T_{\max}(i)$ represent minimum and maximum monthly temperature for the time lag period (τ_1, $\tau_{\min}$) and (τ_2, $\tau_{\max}$), and $\sum_{i=\tau_3}^{\tau_R} R_{\text{ain}}(i)$ represents monthly rainfall for (τ_3, τ_R). $\sum_{i=\tau_1}^{\tau_{min}} T_{\min}(i) \times \sum_{i=\tau_3}^{\tau_R} R_{\text{ain}}(i)$ represents the interaction of minimum temperature and rainfall.

Eq. **1** allows for testing two alternative hypotheses. The first hypothesis is that malaria dynamics were primarily determined by the autoregressive effect (i.e., number of malaria outpatients at time *t* is determined by the malaria incidences in previous months) and

seasonality. In this case, f should account for most variance in malaria outpatient time series data. The alternative hypothesis is that climate variability should be the most important factor if the majority of the variance in the number of malaria outpatients is contributed by g.

The effects of autoregression, seasonality, and climatic variability on malaria incidences were analyzed by using the following two-step method. In the first step, we assumed $g \equiv 0$ in Eq. **1** (i.e., climate variability plays no role), and we determined the functional form of f by using the forward stepwise regression method. The proportion of variance in malaria temporal variation accounted for by autoregression and seasonality was calculated. In the second step, we subtracted the predicted effects of autoregression and seasonality from monthly malaria outpatient time series and then performed forward stepwise multiple regression analyses on the residuals to determine the functional form of g and the variance of malaria outpatient time series contributed by meteorological variables, using meteorological data as independent variables. In both steps, only variables that met the 0.05 significance level were entered into the model in the stepwise regression analysis.

Sensitivity analysis. We evaluated the impacts of climate fluctuation on malaria incidences through sensitivity analysis, assuming political and socioeconomic factors remain the same. The scenarios included (*i*) monthly temperature increase by 1–3.5°C in February–April (the range of mean global land surface temperature increase by year 2100 predicted by the Intergovernmental Panel on Climate Change) (28); (*ii*) rainfall increase by 22% (the average fluctuation of rainfall in April and May during 1961–1990 for the seven study sites); and (*iii*) changes in both temperature and rainfall simultaneously. The predicted change in the number of monthly malaria outpatients as a result of climatic condition changes was computed as the percentage of changes in malaria outpatient numbers relative to those under the average climatic condition between 1961 and 1990. For simplicity, we reported the changes in the month of June when the number of malaria outpatients generally reaches a peak in our study sites in Kenya and Uganda.

Results

Climate Warming and Climate Variability. We observed substantial anomalies in maximum and minimum monthly temperature and rainfall (Fig. 1 for Nandi; see supporting information, which is published on the PNAS web site, for other sites). Compared to 1978–1988, we found that two sites exhibited small but statistically significant changes in temperature among the seven study sites in 1989–1998, but no sites exhibited significant changes in rainfall between the two periods (Table 2). The site Alaba exhibited a 0.46°C increase in the maximum monthly temperature in 1989–1998 ($P = 0.014$), and Kilgoris showed a 0.19°C increase in the minimum monthly temperature ($P = 0.032$). However, compared to the period of 1978–1988, the average annual variance in the maximum monthly temperature during 1989–1998 significantly increased in five (Alaba, Kericho, Eldoret, Nandi, and Kabale) of the seven study sites (Table 2). Kericho and Eldoret also exhibited significant increases in the average annual variance in the minimum monthly temperature and rainfall, respectively. Only one site (Ziway) exhibited significant reduction in the average annual variance in the minimum monthly temperature. Kilgoris is the only site where we did not detect any significant changes in climate variability.

Association Between Climate Variability and Malaria Incidence. Significant change in climate variability has coincided with increased magnitude (Fig. 1 for Nandi; see supporting information for other sites) and frequency of malaria epidemics since 1989 (Table 2). The cross-correlogram analysis found that monthly rainfall and maximum and minimum temperature were significantly correlated with monthly malaria incidences with a time lag of 1–2 months and 2–5 months, respectively (data not shown). Our estimates of the time

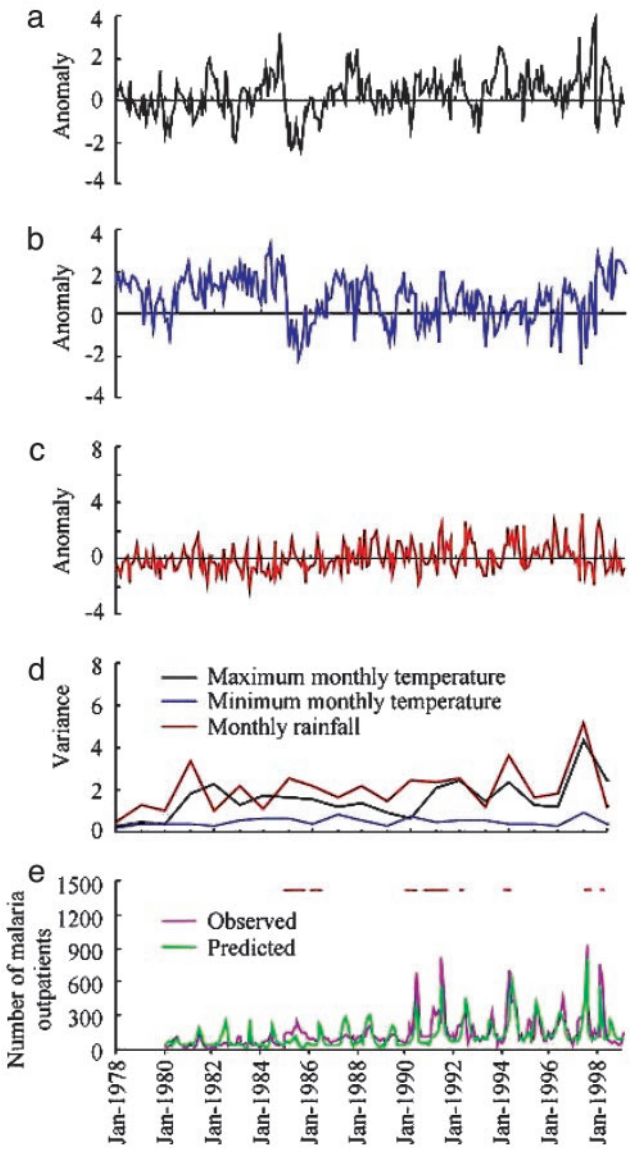

Fig. 1. Meteorological and number of monthly malaria outpatients time series and epidemic alerts in Nandi District Hospital, western Kenya. (*a*) Maximum monthly temperature. (*b*) Minimum monthly temperature. (*c*) Monthly rainfall. (*d*) Annual variance in monthly maximum and minimum temperature and rainfall (rainfall variance was scaled by division by 2,000). (*e*) The number of monthly malaria outpatients. Dashed lines stand for the months that epidemic alerts were declared by the Cullen's method. Meteorological parameters were represented by standardized anomaly relative to the 1961–1990 mean for each site. See Table 1 for source of number of malaria outpatients data. For a comprehensive list of time series data of other study sites, see supporting information.

delay in the association between malaria incidences and temperature and rainfall were consistent with previous studies in Rwanda (8) and Kakamega, western Kenya (18).

Similar to the cross-correlogram analysis, the time series analysis revealed some effects of autoregression: Malaria outpatient number generally exhibited significant and positive correlations with the number of malaria outpatients of the past 1–2 months (Table 3). Such a lagged, compensatory lag effect reflects the temporal effects of a malaria epidemic because an increased number of *P. falciparum* gametocyte carriers is expected after a large number of cases. A 5-month-lag compensatory lag effect was detected in one site (Alaba), likely caused by the factor that malaria transmission has two peaks a year; the interval between the two peaks was 5 months.

Table 2. Decadal average and variance of monthly temperature and rainfall and total number of epidemic months detected by the Cullen's method in seven East African highland study sites

Site	Variables	Decadal average*				Average annual variance†				Proportion of epidemic months, %	
		1978–1988	1989–1998	*t*	*P*	1978–1988	1989–1998	*t*	*P*	1978–1988	1989–1998
Alaba	Maximum temperature	25.96	26.42	2.44	0.014	3.52	4.64	1.96	0.033	0	7.5
	Minimum temperature	12.62	12.63	0.02	0.491	3.95	3.74	0.43	0.338		
	Rainfall	54.99	52.46	0.53	0.301	4.92	4.22	0.60	0.279		
Ziway	Maximum temperature	25.77	25.83	0.30	0.379	3.42	4.26	1.48	0.078	NA	7.5
	Minimum temperature	12.58	12.82	1.11	0.139	4.27	3.14	3.08	0.004		
	Rainfall	52.15	53.30	0.16	0.443	4.92	4.79	0.09	0.462		
Kericho	Maximum temperature	22.68	23.17	1.39	0.091	1.43	3.59	4.54	<0.001	6.8	11.7
	Minimum temperature	10.91	11.19	1.40	0.091	2.36	3.90	1.91	0.040		
	Rainfall	151.51	133.92	1.14	0.143	6.02	7.48	1.04	0.157		
Kilgoris	Maximum temperature	25.56	25.81	1.67	0.057	2.80	2.33	1.26	0.113	4.6	8.3
	Minimum temperature	15.77	15.96	1.98	0.032	0.92	0.84	0.97	0.174		
	Rainfall	102.30	110.10	1.19	0.129	2.70	2.35	0.77	0.226		
Eldoret	Maximum temperature	23.19	23.29	0.58	0.290	1.54	2.22	2.54	0.011	0	10.0
	Minimum temperature	10.99	10.73	1.41	0.092	0.93	1.30	1.51	0.074		
	Rainfall	73.08	86.04	1.36	0.087	3.06	5.06	2.54	0.011		
Nandi	Maximum temperature	25.48	25.84	1.60	0.069	1.25	1.91	1.77	0.047	9.3	15.9
	Minimum temperature	13.57	13.32	1.40	0.091	0.46	0.48	0.20	0.422		
	Rainfall	111.60	126.00	1.61	0.065	3.36	4.66	1.40	0.089		
Kabale	Maximum temperature	23.55	23.33	0.85	0.202	0.71	1.06	2.11	0.024	NA	3.1
	Minimum temperature	12.14	12.32	1.10	0.138	0.54	0.68	0.95	0.179		
	Rainfall	88.91	95.23	0.59	0.282	2.12	3.30	1.58	0.073		

NA, not applicable.
*Temperature unit is °C, and rainfall unit is millimeters (mm).
†Rainfall variance value listed in the table is the actual variance divided by 2,000.

We have statistically factored out the contribution of autoregression, seasonality, and climate variability to the temporal variation of malaria incidence. Eighteen to 63% variance (mean = 38.6%) in the monthly malaria outpatient time series data were attributed to autoregression and seasonality (Table 3). The net variance in the number of malaria outpatients time series because of climate variability varies considerably among sites, ranging from 12% to 63% (mean = 36.1%). Climate variability contributed more variance than autoregression and seasonality in three (Kilgoris, Kericho, and Eldoret) of seven sites (Table 3). For all seven sites studied, we found significant and positive effects of interactions between maximum or minimum monthly temperature and rainfall on the number of malaria outpatients, suggesting synergistic effects of climatic conditions on malaria transmission.

Sensitivity Analysis. Our model accounted for 65–81% of the total variance in the number of malaria outpatients time series data for the seven study sites, an outstanding fit of the observed malaria outpatient time series (Fig. 1). We therefore used the model to evaluate the impacts of climate fluctuation on malaria incidences

Table 3. Model fitting results and the effects of autocorrelation, seasonality, and climate variability on the temporal variance in the number of monthly malaria outpatients in seven East African highland sites

Site	Stepwise multiple regression to test the effects of autocorrelation and seasonality						Stepwise multiple regression to test the effects of climate variability						
	α	*d*	β	b_1	b_2	r^2 (autocorrelation and seasonality)*	γ_1	γ_2	γ_3	γ_4	γ_5	r^2 (climate variability)†	r^2 (total)‡
Alaba	49.75	1	0.64	–	–	0.63	–	–	–	–	90.85	0.12	0.75
		5	0.25										
Ziway	126.78	1	0.60	–	–	0.38	−104.79	–	–	1.28	–	0.27	0.65
Kericho	19.79	1	0.36	–	–	0.19	–	−17.95	−1.46	–	6.43	0.59	0.78
Kilgoris	200.95	1	0.58	–	–	0.18	–	−1,137.52	−187.49	–	771.97	0.63	0.81
Eldoret	335.54	1	0.41	–	181.50	0.33	–	−375.91	−38.13	–	172.06	0.44	0.77
		2	0.20										
Nandi	89.12	1	0.71	65.62	37.15	0.58	–	–	−6.42	33.40	–	0.16	0.74
Kabale	168.85	1	0.76	–	–	0.41	–	–	−11.87	–	52.91	0.32	0.73
		2	−0.39										

Parameter α is the deterministic drift. *d* is the time lag in months selected by equation 2. β, b_i, and γ_i are regression coefficients determined by the stepwise regression analysis. For both steps, only variables that met the 0.05 significance level were entered into the analysis. – refers to those variables not entered into the analysis.
*r^2 (autoregression) represents the variance of monthly malaria outpatient time series attributed to autocorrelation and seasonality.
†r^2 (climate variability) refers to the variance of monthly malaria outpatient time series attributed to climate variability.
‡r^2 (total) refers to the total variance of monthly malaria outpatient time series accounted for by autocorrelation, seasonality, and climate variability.

Table 4. Sensitivity analyses of the effects of climate variability on malaria outpatient numbers in the East African highlands

Site	Average climatic conditions 1961–1990			Scenarios of climate changes and resulting increases of malaria cases (in percentage) in the month of June in relation to average climatic conditions				
	Monthly maximum temperature, °C*	Monthly minimum temperature, °C*	Monthly rainfall, mm*	Increase temperature by 1.0°C†	Increase temperature by 3.5°C†	Increase rainfall by 22%	Increase temperature by 1.0°C and rainfall by 22%†	Increase temperature by 3.5°C and rainfall by 22%†
Alaba	25.86	10.73	117	9	33	22	34	62
Ziway	28.16	13.11	63	8	27	138	156	201
Kericho	27.10	10.33	227	37	129	94	151	295
Kilgoris	27.51	13.16	203	32	111	35	78	184
Eldoret	24.65	9.75	121	21	71	118	186	357
Nandi	27.51	12.03	203	95	332	6	122	411
Kabale	21.31	10.99	149	77	269	6	100	334

*Monthly maximum and minimum temperature and rainfall data presented in the table are for the months significantly correlated with the number of malaria outpatients through the cross-correlogram analysis.

†Temperature increase refers to increase in both maximum and minimum temperature.

using sensitivity analysis, assuming political and socioeconomic factors remain unchanged. We found that a 1°C increase in the minimum and maximum monthly temperature would lead to an 8–95% increase in the number of malaria outpatients in the month of June from average climatic condition (Table 4). A temperature increase by 3.5°C would result in a 27–332% increase in malaria incidences. The sites most sensitive to temperature change (Nandi and Kabale) exhibit a lower average maximum or minimum monthly temperature. A monthly rainfall increase of 22% would lead to a 6–138% increase in malaria incidence. The site most sensitive to rainfall change (Ziway) also shows the lowest rainfall. The effects of increases in temperature and rainfall on malaria incidences are synergistic. In Eldoret, for example, a 71% and 118% increase in malaria is expected if temperature and rainfall are increased by 3.5°C and 22%, respectively; however, a 357% increase in the number of malaria outpatients is predicted if both variables change simultaneously (Table 4).

Discussion

In this study, we found that two of seven sites exhibited a small but statistically significant temperature increase during 1989–1998 in comparison to 1978–1998. However, five of seven sites showed a significant increase in climate variability measured by the average annual variance in the temperature and/or rainfall. Our analysis of climate change, based on actual meteorological records, suggests that climate warming has occurred only on a small geographic scale, but increased climate variability, whether natural or anthropogenic, has occurred on a larger geographic scale in the East African highlands. A high frequency of extreme climate events, such as El Niño and drought in Africa since the late 1980s, has been reported (38–40). Our results on the nonsignificant mean temperature changes over the past two decades in Kericho was consistent with the finding of other studies (22, 29).

One marked characteristic of the malaria situation in the 1990s in the East African highlands is that both the frequency of malaria epidemics and the number of malaria outpatients in an epidemic have dramatically increased compared to those in the 1980s. Are more frequent malaria epidemics in the 1990s causally coincident with increased climate variability? Through joint analysis of epidemiological and climatological time series, we have statistically factored out the contribution of autoregression, seasonality, and climate variability to the temporal variation in the number of malaria outpatients. We demonstrated that climate variability is strongly associated with the number of malaria outpatients in three Kenyan sites (Kericho, Kilgoris, and Eldoret), where climate variability contributed >40% of the temporal variance in malaria outpatient numbers, far more than the contributions from autoregression and seasonality. For all seven study sites, we found highly significant nonlinear, synergistic effects of the interaction between rainfall and temperature on malaria incidence, indicating that the use of either temperature or rainfall alone is not sensitive enough for the detection of anomalies that are associated with malaria epidemics (18, 22, 29). Thus, assessing the impact of climate change on malaria transmission requires consideration of not only annual mean temperature changes, but more importantly, the extent of temperature and rainfall interannual variability.

We have demonstrated a high degree of spatial variation in the sensitivity of malaria outpatient numbers to climate fluctuations. Climate factors contributed <20% of the temporal variance in the number of malaria outpatients in two sites, Alaba and Nandi (Table 1). Therefore, malaria dynamics are largely driven by autoregression and/or seasonality in these sites, and case surveillance is important for predicting malaria outpatient dynamics. The observed large among-site variation in the sensitivity to climate fluctuations may be governed by complex interactions between climate and biological and social factors. Potentially important factors include land use, topography, *P. falciparum* genotypes, malaria vector species composition, availability of vector control and healthcare programs, drug resistance, and other socioeconomic factors (41–44). These factors may have significant location-specific effects. Discerning the contributions of these factors will be particularly useful for assessing the vulnerability of public health systems to climate variability.

This study demonstrates the important role of climate variability in malaria dynamics in some highland sites. However, malaria transmission involves complex interactions between *Plasmodium* parasites, anopheline mosquitoes, and humans. What pathways are being affected by climate variability and cause frequent epidemic malaria in the highlands? We propose the following conceptual model to illustrate the pathways leading to epidemic malaria in the East African highlands. The East African highland region contains numerous valleys and basin-like depressions in a plateau where malaria transmission intensity ranges from low to a level as high as the lowland (9). Human settlers in these foci are the main malaria reservoir, and they develop some degree of immunity to the severe consequences of malaria infection, whereas the human population uphill is not exposed to malaria infection regularly and generally lacks immunity to malaria. The valleys and basin-like depressions were recognized as less desirable areas to live; the human density in these foci was relatively lower. As a result of rapid human population increases over the past four decades in the East African highlands (http://grid2.cr.usgs.gov/globalpop/africa/app-2.php3), however, there have been unprecedented human settling pattern and land-use changes (45, 46). More families have settled in these

less desirable areas and thus have dramatically increased malaria reservoir size. Land-use changes have created more mosquito breeding sites and have changed the water chemistry and temperature of mosquito larval habitats so that mosquito larval development is accelerated and survivorship increased (25, 47). They have also altered the microclimate of the adult mosquitoes and accelerated malaria parasite development (25). When the ambient temperature and rainfall is suitable for a short period, mosquito population size and parasite sporogonic development rates, and thus, mosquito vectorial capacity (48), increase rapidly. People living in the valleys receive more infective bites under such ambient conditions, but only a small proportion of residents, particularly young children, develop symptomatic malaria because of their functional immunity. An epidemic arises when people living uphill are being infected by malaria parasites through locally bred mosquitoes or mosquito dispersal; because they lack functional immunity, they are very vulnerable to malaria infection and often develop symptomatic or even severe malaria. Human mortality is increased when drug resistance, inadequate administration of drugs, failure to seek treatment or delayed treatment of malaria patients, and HIV infections in the human population become increasingly prevalent (9, 15, 22, 49, 50).

Our model postulates that climatic condition is one crucial factor in initiating an epidemic, but topography, human settlement pattern, land use, and drug resistance are also important. Climate conditions influence the development, reproduction, and survivorship of anopheline mosquitoes and malaria parasites. Topography and human settlement patterns affect the spatial distribution of mosquitoes and susceptible and immune human populations. Land-use changes can cause the environmental conditions to be more favorable for the development and reproduction of mosquitoes and parasites. Drug resistance aggravates malaria case fatality after an epidemic is initiated. Our model predicts that, in the highlands, most severe malaria cases during an epidemic come from uphill human populations that have not been regularly exposed to malaria infection. The model, if validated by epidemiological and entomological data, suggests several potential approaches for preventing or controlling malaria epidemics in the highlands. For example, targeted control of malaria vectors, using larvicides at the larval stage and using adulticides at the adult stage, in the valleys and basin-like depressions in a plateau may be a cost-effective approach to reduce malaria transmission. Malaria transmission in the valley can be further reduced if insecticide-based mosquito control is combined with elimination of larval habitats through appropriate land-use management.

The development and implementation of malaria early warning systems is advocated by the Roll Back Malaria project led by the World Health Organization (51, 52). One main aim of malaria early warning systems is to determine the timing of when an epidemic will occur so that timely responses to prevent and contain malaria epidemics can be formed. Despite high spatial variability in the sensitivity of the number of malaria outpatients to climate fluctuation, our results suggest that development of reliable malaria early warning systems in the highlands is possible if we take into consideration case surveillance data, temperature and rainfall climate variability, and other factors underlying the observed spatial variability.

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