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Author(s): Luis Fernando Chaves and Constantianus J. M. Koenraadt
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CLIMATE CHANGE AND HIGHLAND MALARIA: FRESH AIR FOR A HOT DEBATE

LUIS FERNANDO CHAVES
Department of Environmental Studies, Emory University, Atlanta, GA 30322 USA
E-MAIL: LFCHAVE@EMORY.EDU

CONSTANTIANUS J. M. KOENRAADT
Laboratory of Entomology, Wageningen University, Wageningen, The Netherlands
E-MAIL: SANDER.KOENRAADT@WUR.NL

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ABSTRACT

In recent decades, malaria has become established in zones at the margin of its previous distribution, especially in the highlands of East Africa. Studies in this region have sparked a heated debate over the importance of climate change in the territorial expansion of malaria, where positions range from its neglect to the reification of correlations as causes. Here, we review studies supporting and rebutting the role of climatic change as a driving force for highland invasion by malaria. We assessed the conclusions from both sides of the argument and found that evidence for the role of climate in these dynamics is robust. However, we also argue that over-emphasizing the importance of climate is misleading for setting a research agenda, even one which attempts to understand climate change impacts on emerging malaria patterns. We review alternative drivers for the emergence of this disease and highlight the problems still calling for research if the multidimensional nature of malaria is to be adequately tackled. We also contextualize highland malaria as an ongoing evolutionary process. Finally, we present Schmalhausen's law, which explains the lack of resilience in stressed systems, as a biological principle that unifies the importance of climatic and other environmental factors in driving malaria patterns across different spatio-temporal scales.

THE 1957 Cold Spring Harbor Symposium on Quantitative Biology is widely known among ecologists as the setting for one of the most heated debates in the history of population ecology. This debate pitted proponents of exogenous factors as mechanisms behind population regulation against those who emphasized endogenous factors. This argument can especially be seen in the open discussions of the symposium seminars led by Birch (1957) and Andrewartha (1957), in which they presented examples illustrating the importance of exogenous, density-independent drivers (e.g., climate

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variables such as rainfall or temperature) on the distribution and abundance of insect populations. Some of these arguments were questioned by Nicholson (1957) with his laboratory results on blowflies. His work supported the hypothesis that endogenous, density-dependent factors (e.g., number of individuals) can drive animal population dynamics through changes in the life history traits of individuals that have experienced different levels of crowding. This debate prompted significant research efforts in population ecology in the decades that followed. Today, the synthesis and abstraction of observation acknowledges that populations have a self-regulatory component (negative feedback), that the endogenous component of Nicholson is always present, and that exogenous forces also influence the fate of a population; therefore, both factors are needed to explain population dynamics (Turchin 2003). Infectious diseases, as phenomena involving organisms and their environments, raise the same questions that have been the object of study of ecologists for a long time. For example, what determines the spatial distribution and prevalence of certain diseases? What factors are responsible for their reemergence, and how do these factors interact? Infectious diseases that are transmitted from person to person by vectors (e.g., mosquitoes, sand flies, and ticks) are the most challenging, since both exogenous and endogenous factors could act on the vector and the disease agent, as well as the humans ultimately infected by the disease agent (Macdonald 1953).

The proposition that climate is responsible for the distribution and abundance of insects (Andrewartha 1957; Birch 1957) such as mosquitoes, together with the realization of climate change by the scientific community, has prompted some scientists to forecast an expansion of the current malaria distribution and an increase in its burden following a rise in temperature (e.g., Patz et al. 2002; Pascual and Bouma 2009). However, factors regulating the abundance and distribution of malaria are multivariate and complex (e.g., Macdonald 1953; Lindsay and Birley 1996). In fact, malaria has been absent for some time from areas that harbor large populations of competent mosquito vectors and with environmental conditions conducive to parasite development and transmission. Malaria has also been endemically present in places with the most adverse conditions for parasite transmission, which shows that, at best, the consideration of climate alone will lead to a rough approximation of malaria's geographical range and that other factors can influence its distribution within or beyond the boundaries that an optimally suitable environment could suggest. For example, it is well-documented that the Romans knew the relationship between marshes and "malaria-like" fevers, and this knowledge informed their selection of places for new settlements and military camps. Early human history is full of battles that were won with the aid of malaria as an additional platoon attacking enemies (de Zulueta 1987; Najera 1994). Even during the coldest years of the Little Ice Age (1560s to 1730s), reports of malaria outbreaks in England and Scotland were common. In England, epidemics were associated with years of high famine (Reiter 2000), and, in Scotland, the largest epidemics happened during the warmest and wettest summers of this period (Duncan 1993). Malaria was also common in Scandinavian countries during the 19th century (Reiter 2008). After World War II, malaria endemic transmission was erased from the USA (Humphreys 2001), and, since 1973, Europe has been declared free of the disease (de Zulueta 1987, 1994). In 1981, Australia—a large subtropical area—also achieved "malaria-free" status (Bryan et al. 1996).

Unfortunately, the pattern of waning malaria seen in the USA, Europe, and Australia is not globally widespread. Today, a child dies of malaria every 40 seconds, and between one and three million people die each year around the world, primarily in sub-Saharan Africa (Sachs and Malaney 2002). Although these figures depict spatially coarse patterns, they do not reveal the fact that spatially fine patterns have been changing. Such patterns are quite evident in the geographical malaria hot spot that is the focus of this paper: the sub-Saharan African highlands. These highlands are sparse land extensions in several African countries, with altitudes of at least 1200 m (Lindsay and Martens 1998).

Historically, the African highlands have been used as a shelter against malaria. In this context, it is important to note that every 100 m increase in altitude is associated with a 0.6 °C decrease in temperature (Strahler 1973). Also, malaria parasites do not develop inside their mosquito host if temperatures fall below 15 °C (Patz and Olson 2006). Thus, malaria has been naturally excluded from these areas, most likely because they experience conditions that limit the biology of the parasite (Lindsay and Martens 1998).

In the past, malaria transmission in the East African highlands was mainly sporadic and unstable (i.e., epidemic). Nevertheless, since the second half of the 20th century, this pattern has changed, with an increase in the frequency of epidemic outbreaks (Lindsay and Martens 1998; Pascual et al. 2008; Shanks et al. 2005). Malaria invasion of highlands is not restricted to sub-Saharan Africa, but is globally widespread. It has also invaded the highlands of Indonesia (Anthony et al. 1992), Papua New Guinea (Mueller et al. 2005), Madagascar (Bouma 2003), and Afghanistan (Rab et al. 2003).

The absence of a common pattern leading to the emergence or extinction of this disease has created an intense debate over the main determinants of malaria resurgence in the East African highlands. In this review, we start by presenting the effects of the different elements of climate (temperature, rainfall, and humidity) and the natural environment (breeding sites, vegetation) on the entomological parameters relevant for malaria transmission. We then re-analyze data that support warming trends in the East African highlands, where malaria is expanding its geographical range. In this respect, we also address the possible differences between the effects of climatic trends and climatic variability on malaria transmission. Because the current global distribution shows that malaria has not expanded into areas as previously forecasted by modelers, we also review other important factors that are considered robust predictors of malaria transmission—primarily demographic drivers and land use change. In the final two sections, we present Schmalhausen's law as an epistemological tool for understanding the contradictory effects of climatic drivers at the local scale of transmission, and to also better our understanding of the effects of all the relevant factors for malaria transmission at the different evolutionary and ecological spatiotemporal scales of this disease.

Entomological Parameters and the Plausibility of Climate Change Driving Malaria Resurgence in the African Highlands

Since Ronald Ross's (1897) discovery of mosquitoes as vectors of malarial parasites, many attempts have been made to understand the eco-epidemiology of the disease and the risk to which humans are exposed. The first major step was the introduction of the "basic reproduction rate" (Macdonald 1953), which expresses the number of new cases originating from a single case of malaria in the absence of immunity (Table 1). By leaving out the parasitological aspects of the equation, Garrett-Jones (1964) introduced the concept of "vectorial capacity" (C), which provides a theoretical framework for calculating the number of expected inoculations of man per infective case per day. Most parameters of these equations are difficult to measure under field conditions, and it is therefore more convenient to express the level of malaria transmission as the "entomological inoculation rate" (EIR), or the number of infective bites per person per day (Onori and Grab 1980). Public health surveys may also gather data related to the actual outcome of the intensity of transmission—i.e., the number of infected hosts (parasite prevalence), sick cases in the host population (morbidity), and deaths (mortality). All these may be used to compare transmission dynamics between areas, such as highland and lowland areas.

Various efforts have been made to study the relationship between malaria risk parameters. These have shown that EIR can be used to predict levels of parasite prevalence (Beier et al. 1999) and mortality

TABLE 1

Overview of malaria risk parameters

Malaria risk parameter	**Definition**	**Mathematical expression**
Basic reproduction rate	Number of secondary infections originating from a primary case in the absence of immunity	$ma^2 \, bp^{n} / -r \, (\ln p)$[#]
Vectorial capacity	Number of secondary inoculations of man per infective case per time unit	$ma^2 \, p^{n} / -\ln p$[†]
Entomological inoculation rate	Number of infective bites per person per time unit	$ma^{*} \, s$[‡]

Source: Macdonald (1953)[#]; Garrett-Jones (1964)†; Onori & Grab (1980)‡.

Explanation of parameters:
a = Man-biting habit
m = Mosquito density relative to man
b = Susceptibility of mosquito to parasite infection
p = Daily mosquito survival
n = Incubation period of parasite in mosquito
r = Recovery rate from infection
s = Sporozoite rate (proportion of infected mosquitoes)

(Smith et al. 2001), although others have argued that this relationship may not be valid, as some epidemiological settings may have been under-represented in the meta-analyses (Trape et al. 2002). The use of different mosquito collection techniques, the estimation of yearly EIR from monthly EIR, and the level of natural acquired immunity in the population may all lead to the variation observed in these studies. However, despite these variations, it can still be asserted that studying the effects of climate on the entomological parameters of malaria transmission should be the initial step to understanding possible impacts of changing environments on this disease. In the following sections, we present a detailed account of the effects of temperature, rainfall, humidity, distance to breeding sites, and vegetation on malaria.

TEMPERATURE

Development of *Plasmodium falciparum* in the mosquito host takes approximately 9–10 days at a temperature of 28 °C, while development ceases when temperatures drop below 16 °C (Macdonald 1953). Larval populations of *Anopheles gambiae*, the major vector of *P. falciparum* in Africa, will not develop into adults when ambient temperatures drop below ~16 °C (Jepson et al. 1947), and daily survival of adults reaches zero at around 40 °C (Lindsay and Martens 1998). A higher temperature leads to a higher digestion rate of the bloodmeal, which results in more frequent vector-host interactions. Combining the survival of the mosquito population (p) and the development time of the parasite (n) gives us the proportion of mosquitoes that survives the incubation period of the parasite (p^n) (Table 1). The highest proportions surviving the intrinsic incubation period can be found between 28 and 32 °C (Craig et al. 1999).

In the field, both minimum and maximum temperatures have been related to the abundance of vector populations: higher minimum temperatures led to increased vector densities in the highlands of Uganda (Lindblade et al. 2000), while higher maximum temperatures were correlated with lower biting rates in western Kenya (Patz et al. 1998). Interestingly, Minakawa et al. (2002b) found that two sibling species of the *An. gambiae* complex, *An. gambiae sensu stricto* and *An. arabiensis*, were differentially sensitive towards ambient temperatures; higher maximum temperatures were associated with higher densities of *An. arabiensis*, whereas higher minimum temperatures were related with lower densities of *An. gambiae s.s.* This is in accordance with other findings on this species complex, whereby *An. gambiae s.s.* performs better under cooler conditions (Petrarca et al. 1991; White 1972). Other studies did not find a clear relationship between temperature, on the one hand, and vectorial capacity or entomological inoculation rate on the other (Lindblade et al. 2000; Shililu et al. 1998), perhaps as a result of the presence of other confounding factors.

Numerous efforts have been made to link temperature directly to malaria incidence rates throughout the African continent (Bouma 2003; Craig et al. 2004; Kleinschmidt et al. 2001; Mabaso et al. 2007; Shanks et al. 2002; Ye et al. 2007; Zhou et al. 2004). These have used various statistical modelling approaches and considered mean, maximum, and minimum temperatures, as well as deviations from long-term averages (anomalies) and lag times (see below for a discussion on the use of statistical tools and inferring conclusions from data). Although there is no consensus on a single, most valuable temperature predictor for malaria risk, we argue that each ecological setting requires its own validation of temperature and an assessment of how it can be included in predictive models.

RAINFALL

Many African malaria vectors are dependent on rainfall, since they prefer to breed in small temporary sites created by the rains (Gillies and Coetzee 1987). It is therefore not surprising that in the early days of malaria research, the onset of rainy seasons was associated with increased vector densities and malaria cases (Garnham 1929; Gill 1920; Haddow 1942; Holstein 1954). However, the lack of powerful tools (e.g., statistical tools and those used for gathering geographic information) made it hard to quantify the relationship with respect to spatial and temporal variation in rainfall patterns. Today, the amount of weekly rainfall has been correlated with the abundance of larval habitats with a time lag of one week and with vector densities inside local houses with a lag of two weeks (Koenraadt et al. 2004a). The monthly rainfall anomaly (i.e., the deviation in rainfall from the month's historical average) was correlated with vector density one month later (Lindblade et al. 1999).

As with temperature, numerous studies included rainfall as a direct predictor of malaria incidence (Binka et al. 1994; Craig et al. 2004; Drakeley et al. 2005; Githeko and Ndegwa 2001; Kazembe 2007; Kleinschmidt et al. 2001; Mabaso et al. 2007; Shililu et al. 2003; Ye et al. 2007; Zhou et al. 2004), but the relationship between rainfall and malaria risk is not always present (la Grange 1995; Lindblade et al. 1999; Shanks et al. 2002; Shililu et al. 1998). This may be caused by the fact that certain vectors of malaria, such as *An. funestus*, are less dependent on rainfall, since they prefer to breed in more permanent habitats (Gillies and Coetzee 1987). For example, Mabaso et al. (2007) found that rainfall was an important determinant of seasonality in EIR, but not so in areas characterized by two rainfall peaks or irrigation activities. The distribution of rains over the year, the condition of the soil before the rains actually start, and the soil water holding capacity may also obscure correlations (Kazembe 2007).

HUMIDITY

Humidity determines the life span of the mosquito and, thus, its capability to transmit the malaria parasite (Clements 1999). Humidity is a direct product of rainfall and temperature, since these govern the amount of water available and the amount of water the atmosphere can hold, respectively. According to Minakawa et al. (2002b), a higher moisture index (expressed as the ratio of rainfall over evapotranspiration) was associated with a lower density of *An. arabiensis*, as consistent with earlier experimental findings that this species performs better at lower humidity levels (Coz 1973). Soil moisture level was significantly correlated with EIR in western Kenya (Patz et al. 1998), indicating that the water balance—i.e., rainfall − (evapotranspiration + runoff)—plays an important role in determining the number of infective bites people eventually receive. However, relative humidity levels were not related to vector density in a highland area of Uganda (Lindblade et al. 2000), but they were associated with malaria incidence in Burkina Faso (Ye et al. 2007). All this suggests that local variation exists.

DISTANCE TO BREEDING SITES

Malaria has been associated with the presence and proximity of marsh areas—hence the name "mal aria" or "bad air"—since the earliest descriptions of the disease and its symptoms. Studies on the proximity of water bodies, either natural or manmade, showed that indoor vector densities were higher close to breeding sites (Lindsay et al. 1995; Minakawa et al. 2002a; Minakawa et al. 2004) and that malaria risk was, consequently, increased in these areas (Bøgh et al. 2007; Clarke et al. 2002; Ghebreyesus et al. 1999; Kleinschmidt et al. 2001; Lautze et al. 2007; Oesterholt et al. 2006; Staedke et al. 2003; Trape et al. 1992). Interestingly, Clarke et al. (2002) noted that, although risk in terms of exposure was decreased farther away from water bodies, clinical illness was more common, probably as a result of reduced immunity due to lower exposure to infective bites. These studies all suggest that control of larval breeding sites may contribute significantly to a decreased risk of malaria, and larval control strategies should therefore play an integral role in fighting this disease (Killeen et al. 2002).

VEGETATION

Vegetation provides shelter and suitable resting sites for mosquitoes, and it also creates microhabitats in which temperature and humidity conditions are more suitable than in areas without vegetation (Clements 1999). The presence of vegetation may therefore enhance mosquito longevity. The advancement of satellite imagery has made it possible to quantify the amount of photosynthesizing vegetation by means of the normalized difference vegetation index (NDVI), which is based on the absorption and reflection of light waves of different lengths. Positive correlations have been found between NDVI and the bite rate among humans for *An. gambiae* (Patz et al. 1998), as well as between NDVI and malaria prevalence/incidence (Gomez-Elipe et al. 2007; Hay et al. 1998; Thomson et al. 1999). These correlations most likely arise as a result of the close relationship between temperature and rainfall, on the one hand, and vegetation growth on the other. However, another study did not find any correlation between vector abundance and NDVI (Shililu et al. 2003).

TIME SERIES ANALYSIS AND THE CONTROVERSY ABOUT THE EFFECT OF CLIMATE ON MALARIA

Evidence for global climate change greatly relies on accurate observations of weather variables. Thus, given the limited opportunities for manipulation of observations, it is critical for inferences to be robust. Robustness, or the confidence in the certainty of one's result, given that assumptions about such phenomenon might be wrong or untestable, can be evaluated through the agreement of results obtained with different methods or with different models used to analyze the data (Levins 1966, 2006).

Research that supports that the emergence of malaria in the African highlands over the last fifty years is not related to climate change relies on inferences from two methods of data analysis. First, low spectral power (variance) was found for periods of time longer than one year in a spectral density analysis of temperature and rainfall time series from weather stations at Kericho, Kenya (Hay et al. 2000). Second, parametric trends for climate variables from local weather stations and from data interpolated using geographical information systems (GIS) tools were not statistically significant (Hay et al. 2002a; Shanks et al. 2002; Small et al. 2003).

Time series analysis can be performed in the time domain, the frequency domain, and the time-frequency domain. In equations of the time domain approach, the value of the variable under study is predicted from its previous values (Brockwell and Davis 2002). The frequency domain looks for cyclic regularities in time series, while the time-frequency domain shows how the cycles of a time series develop (Shumway and Stoffer 2000). In our supplementary material (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB), a glossary of technical terms related to time series analysis is presented.

In the time domain, one regression model was used to test for trends in climate and malaria suitability (Hay et al. 2002a; Shanks et al. 2002):

$$\Delta y_t = \alpha + \beta t + \gamma y_{t-1} + \sum_{i=1}^{p} \delta_i \Delta y_t + \sum_{j=1}^{12} \mu_j d_j + \varepsilon_t, \quad (1)$$

and a slightly modified version (Small et al. 2003)

$$\Delta y_t = \alpha + \beta t + \gamma y_{t-1} + \sum_{i=1}^{p} \delta_i \Delta y_t + \varepsilon_t, \quad (2)$$

where y is the variable of interest, α, δ, γ are regression parameters, β is the parameter for a deterministic time trend, and t is the time. Seasonality is included in the model via the sum $\Sigma_{j=1}^{12}\mu_j=0$, and d_j, a dummy variable that takes values of 1 or 0 depending on whether y belongs to the month that is being regressed. ε_t represents a random independently, identically, and normally distributed error, with variance (σ_ε^2) (i.e., $\varepsilon_t \sim N(0,\sigma_\varepsilon^2)$).

This modeling approach tests whether there are unit roots in the autoregressive process ($\gamma = 0$; i.e., the process being nonstationary), as well as deterministic ($\beta \neq 0$) or random trends ($\alpha \neq 0$, given $\beta = 0$). Depending on the hypothesis being evaluated, the statistics used to test it have a normal or an augmented Dickey-Fuller distribution (for details, see Brockwell and Davies 2002). The aforementioned studies did not find statistically significant results for deterministic or random trends; however, error assumptions were not tested adequately. Only one portmanteau test for general serial correlation was performed, whereas autocorrelation should be tested for several time lags. Thus, the time domain evidence against the existence of climate change in the African highlands needs to be revised.

As we mentioned previously, one strategy for achieving robustness in a result obtained from observational data is to test several distinct models. Given that the gridded temperature time series (Hay et al. 2002a; Shanks et al. 2002) used for Kericho, Kenya (0.33°S, 35.37°E, 1700-2200m) is available online (http://www.cru.uea.ac.uk/), we fitted three additional models for this series. For details on the techniques that we used, please see the supplementary material.

Figure 1 shows the results for the nonparametric reconstruction of the third order components of a Singular Spectrum Analysis (SSA), the trends of a State Space Basic Structural Model (BSM), and a Seasonal Auto Regressive (SAR) model. In contrast with the time series analyses described above, the methods we used agree on the existence of positive trends in the temperature of Kericho. Similar results—i.e., positive trends—not shown, were obtained for the other three places studied (Kabale, Muhanga, and Gikongoro) (Hay et al. 2002a), and, in all cases, the assumptions of the parametric models BSM and SAR were not violated.

The frequency domain evidence against exogenous drivers for malaria in the highlands has methodological as well as inferential problems (Hay et al. 2000). The reduced variability (or power) at periods longer than a year is not enough to prove the lack of importance of climatic variables, since this is just a descriptive measure of cycles in the data, not their correlation to other variables. Data were also filtered with time averaging, which is known to erase variability peaks at low frequencies, thus eliminating long period cycles (Shumway and Stoffer 2000). To make proper inferences about the lack of importance of climate in driving malaria dynamics in humans, a bivariate or correlational analysis, such as a phase/coherency analysis, relating malaria incidence and climate data in the frequency domain should have been used (Shumway and Stoffer 2000). However, because this type of analysis was not used, an inference about the relationship between both phenomena cannot be made. In the supplementary material, Figure1S shows, using both frequency and time frequency techniques, that cycles for periods longer than a year are indeed signif-

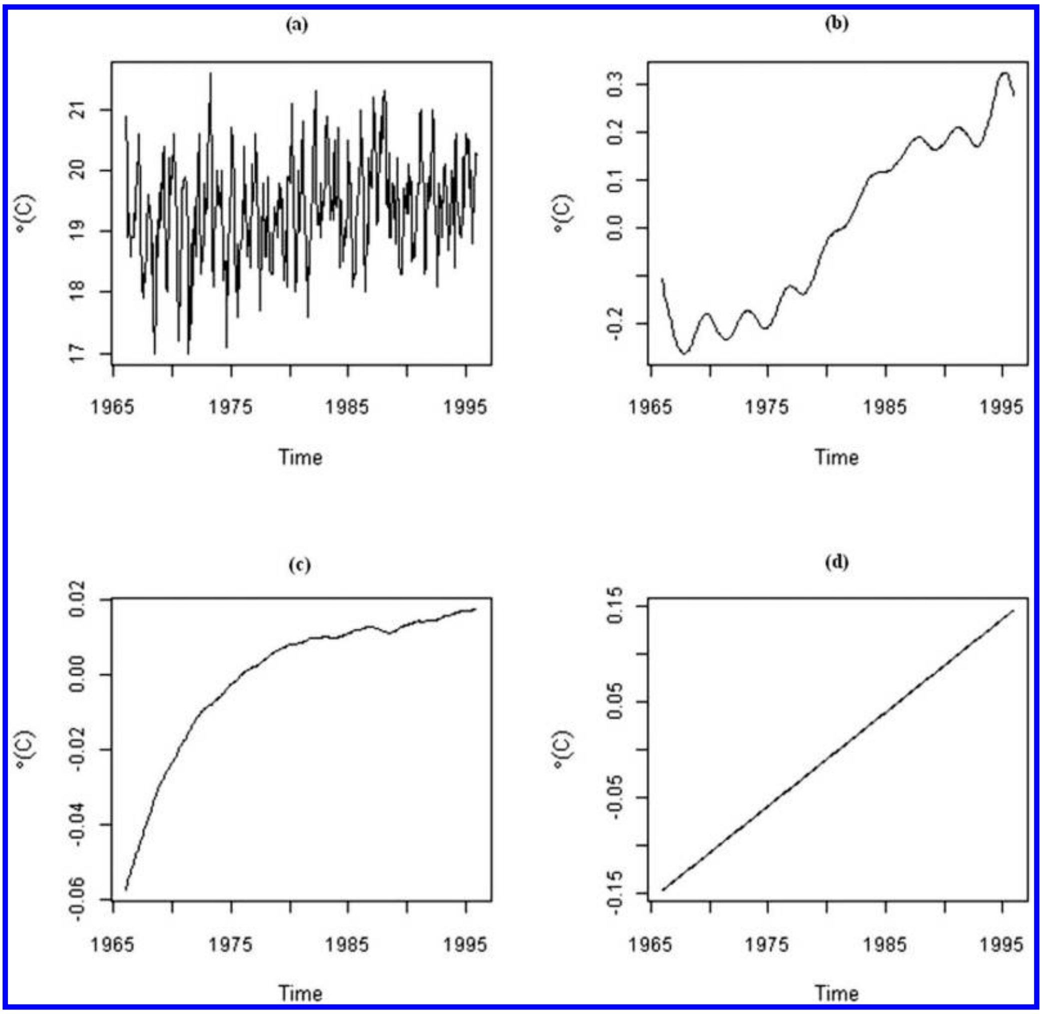

FIGURE 1. KERICHO TEMPERATURE TIME SERIES ANALYSIS IN THE TIME DOMAIN

(a) CRU mean temperature time series for Kericho, Kenya, 1966–2002. (b) Non-parametric trend obtained by reconstructing the third component of a 96 order Singular Spectrum Analysis (SSA). (c) Kalman smoothed Basic Structural Model (BSM) trend. For Kericho, the parameters are:
$\hat{\sigma}^2_\varepsilon = 1.33 \cdot 10^{-2}; \hat{\sigma}^2_\eta = 8.43 \cdot 10^{-2}; \hat{\sigma}^2_\xi = 1.39 \cdot 10^{-5}; \hat{\sigma}^2_\omega = 1.73 \cdot 10^{-2}$.
(d) Linear trend from a Seasonal Auto Regressive (SAR) model. The model fitted was:

$$y_t = \phi_1 y_{t-1} + \sum_{k=12}^{15} \phi_k y_{t-k} - \sum_{j=13}^{16} \phi_1 \phi_{(j-1)} y_{t-j} + \beta(time) + w_t, \text{ where } w_t \sim N(0,\sigma^2_w).$$

The parameters (± SE) are:
$\hat{\phi}_1 = (0.44 \pm 0.05); \hat{\phi}_{12} = (0.20 \pm 0.05); \hat{\phi}_{13} = (0.18 + 0.05); \hat{\phi}_{14} = (0.11 \pm 0.05); \hat{\phi}_{15} = (0.24 + 0.05);$ $\hat{\beta} = (0.0098 \pm 0.0001); \hat{\sigma}_w = 0.31$.
The three trends were normalized to have a mean of zero.

icant, meaning that temperature has longer cycles than the normal seasonality.

In summary, there are elements from all the domains of time series analysis that support an increasing trend in temperature in the highlands of Kericho, as well as the existence of changing interannual cycles in weather; therefore, there is evidence for the existence of climate change in this East African highland area.

The importance of climate is reinforced by the globally widespread pattern of malaria that varies seasonally. Seasonal patterns have been described in India (Madhavan et al. 2001), Pakistan (Bouma et al. 1996), Sri Lanka (van der Hoek et al. 1997), the Sahel (Delmont 1982; Ndiaye et al. 2001), Ethiopia (Abeku et al. 2004), Uganda (Killian et al. 1999), Botswana (Thomson et al. 2005), and South Africa (Craig et al. 2004). Through statistically significant correlation measures, all the studies found an association between increased malaria incidence and increased values of temperature and rainfall; however, none of these studies addressed the issue of weather variability at scales longer than annual.

Supporting the suggestion that "climate change also applies to changes in variability" (Patz et al. 2002:627), several authors have found evidence for changes in local annual, quarterly, or monthly malaria incidences associated with the El Niño Southern Oscillation, or ENSO (Bangs and Subianto 1999; Bouma 2003; Gagnon et al. 2002; Lindsay et al. 2000). ENSO is an interannual climatic phenomenon characterized by an increase in atmospheric pressure and sea surface temperature off the coast of Perú, with an opposite anomaly occurring in the western Pacific Ocean. This phenomenon is strongly associated with several other weather anomalies—primarily, increased or decreased area-specific rainfall (Kovats et al. 2003). Using monthly data from the African highlands, Zhou et al. (2004) also found evidence of climate change by utilizing an entirely different approach. They examined the mean value and variance of annual data from several places grouped into two time intervals, 1978–1988 and 1989–1998. They reported significant differences in the variance of at least one climatic variable in 6 of the 7 places they studied, although the analysis was based on several t-tests. As pointed out by Hay et al. (2005), this approach is flawed, because it underestimates the degrees of freedom for making reliable comparisons. In response to this criticism, Zhou et al. (2005) argued that given their number of tests (a total of 21), the possibility of getting a false rejection to the null hypothesis of no climatic change is reduced, because of multiple testing, to 1 of the 21 tests they performed. However, what matters when making several comparisons is not the significance and the probability of making a type I error—that is, rejecting the null hypothesis when true—but the power of the statistic being used (i.e., the probability of making a type II error, or the likelihood of failure to reject a null hypothesis when false). Also, the study by Zhou et al. (2004) had the limitation of not taking into account the possible spatial correlation between the different climate variables for each place, as well as the possible temporal correlation for each variable.

As argued earlier, it is worth noting that in all the studies we have discussed supporting linkages between climate change and malaria, there is neither a unique climatic pattern nor a unique climate variable associated with the disease. In fact, both the mean value and the variability of such variables appear to be associated with recent changes seen in malaria in the African highlands. The diversity of these results should not be taken as evidence against the influence of exogenous climatic drivers, but instead as an indication of the lack of knowledge on the mechanisms of such linkage.

To illustrate this lack of knowledge, we review four models relating malaria dynamics to climatic variables. The first model was proposed by Teklehaimanot et al. (2004). It included a temporal trend and cited rainfall and temperature as major factors in predicting the number of malaria cases in Ethiopia. This study found mostly positive effects for both temperature and rainfall. A second model by Zhou et al. (2004) included the effect of rainfall, temperature, and their non-additive interaction (i.e., "a synergistic effect"). This model was fitted using inpatient data—i.e., people whose infection was sufficiently severe to require hospitalization—and found both positive and negative effects for rainfall and temperature at different lags. Thus, parameters were obtained for the most severe clinical cases—a fraction of the total number of cases (Malakooti et al. 1998). Additionally, no adjustment for population growth was carried out, thus implying that both population and health facilities had grown at similar rates during the studied period (Zhou et al. 2004). The third model, proposed by Abeku et al. (2004) for data from Ethiopia, developed a linear regression model motivated by classical malaria transmission theory to give a biological interpretation to the statistical approach, in contrast to the two previous models. This model was constructed by assuming that malaria incidence (N) is mainly determined by vectorial capacity (C) in the previous month:

$$N_t = aN_{t-1}^{b}C_{t-1}. \tag{3}$$

In this basic version of the model, a and b are area specific constants, and b ranges from 0 to 1 depending on the area's endemicity (0 for the highest endemicity). The model was parameterized, using temperature and rainfall data, by considering the spatial effects of several counties and ignoring any demography in the populations (e.g., migration or size). This study found positive effects for rainfall and a convex relationship with temperature (mostly postive).

A fourth model was developed by Pascual et al. (2006) in which the life history stages of *Anopheles gambiae* are parameterized as a function of temperature. This model showed that a small change in temperature can amplify mosquito population abundance by several folds. This work also showed a key aspect of the potential effects of climate change on the transmission of malaria and, more generally, on the fate of populations: even if changes in the environment are very small or not even statistically significant, they can be amplified because of the biology of the organisms (Shaman et al. 2002).

These four examples illustrate how different models for different places or aspects of the same phenomenon can find different patterns of association between malaria and climate. As shown in this section, malaria can be correlated, linearly and non-additively through synergistic effects, with several climatic variables at intra- and inter-annual scales. Thus, although the evidence of the linkage between changes in climate and malaria incidence in the African highlands is robust, there is still a lack of knowledge about the ecological mechanisms behind the more phenomenological models. There is an urgent need to investigate if and how generalizations can be made among the diverse results found on the relationship between climatic variables and malaria. For example, malaria in relatively stable climates may be driven more strongly by mean temperature, whereas minimum temperature is a stronger driver for cooler climates, such as highlands. Also, researchers are just uncovering the role of diversity in vector species, of sibling species within species complexes, and of the various chromosomal (based on inversion polymorphisms) and molecular forms of the main vector, *Anopheles gambiae s.s.*, in malaria transmission (della Torre et al. 2005). The consensus on this complexity seems to be that the various forms are incipient species and, thus, in the process of occupying their own niches. Because they are differentially sensitive towards climatic conditions, understanding their biology in relation to malaria transmission and environmental change should hold high priority in future research programs. Table 2 presents further directions for future research in ecological entomology.

Malaria's Neglected Phenomena: The Panclimatic Paradigm

The panclimatic paradigm is the reduction of global vector-borne disease emergence or resurgence, as linked to changes in climate over recent years. This paradigm is the product of reifying results from statistical models applied to study the patterns of association between climate and infectious diseases, or from the successful fitting of mathematical models that include climate variables. Despite evidence, or suggestive observations, for alternative causes behind the emergence and resurgence of malaria, the panclimatic paradigm has been a cliché in the resurgence research agenda for some time now (e.g., Hoshen and Morse 2004; Rogers and Randolph 2000; Tanser et al. 2003; Thomas et al. 2004; Pascual and Bouma 2009). Reiter (2000, 2008) and Reiter et al. (2004) have criticized this argument, emphasizing that the abuse of "climate change" arguments to explain malaria trends in the African highlands is inaccurate. They argue that climate, if associated with this resurgence, is not necessarily the ultimate and only cause of such change. The search for ultimate causes and the focus on the isolated "main drivers" of malaria resurgence in the African highlands is a necessary step in the research process. However, a belief in a unique, isolated, and autonomous main driver is at best an expression of a reductionist approach to understanding nature. This approach is based on the assumption that the understanding of isolated parts will lead to a full comprehension of the entire system that embeds them (Lewontin and Levins 2000). This way of thinking about phenomena is reinforced by the fact that mathematical tools, especially those of statistical data analysis, tend to be reductionistic.

For example, Teklehaimanot et al. (2004) pointed out the instability in parameter estimation by linear models. This instability arises when predictors have a very high linear correlation, close to ± 1. The problem is caused by the unidentifiability of the predictor matrix (Faraway 2005), which does not allow for some necessary manipulation to compute parameters using linear models. Basically, the predictor matrix is near singular, and this produces numerical errors during matrix inversion, ultimately reflecting a constraint of linear algebra. In addition, a model fitted using the framework of linear or generalized linear models will always carry the uncertainty of predictors that can covary with the "causal" predictor, without having any direct effect on malaria transmission. However, there are statistical strategies that may avoid the problems of strongly correlated variables, such as the use of multivariate tools like principal components analysis and multidimensional scaling (e.g., Chaves et al. 2008a). Thus, although the limitations of statistical tools are always present, ways to handle them have been devised. Yet, in any complex system with relatively simple feedback pathways, some perturbations can change the signs of correlations, leading to the absence of correlation or the finding of paradoxical or unexpected relationships (Lewontin and Levins 2000). In fact, it has been widely documented that interactions between organisms can change in sign and magnitude through the dynamic development of their association (Hernandez 1998). Therefore, problems with parameter estimation need to be understood as products of a system that will likely become unstable given any perturbation. The parameters estimated with linear models, which are correct and useful for predictions of the data used to fit the model and to gain insights into the dynamics of disease transmission, need to be presented with caution based upon the stability of the system. By contrast, forecasts or predictions about the future can be very imprecise because of the sensitivity of nonlinear multidimensional systems to all of their underpinnings, especially those that are not accounted for by the studied models.

As a result of the above constraints, the panclimatic paradigm is epistemologically weak, especially since it attempts to make predictions outside its limits of validity when forecasting future scenarios for malaria distribution and incidence based on climate alone. Consequently, the search for alternative malaria drivers has become one of the major fields of inquiry over recent years. The biggest problem with alternative drivers for malaria resurgence is that they have not been quantified and, in general, there is not a good understanding of their dynamic mechanisms (Jones and Williams 2004). As presented by Wilson (1994), diseases in humans show patterns of emergence and resurgence resulting from new cultural practices, new patterns of human migration, biological invasions of pathogens and vectors, and environmental change (widely defined and not restricted to climate). The plausibility of other drivers behind the global resurgence of malaria has been widely acknowledged. The pioneering work of MacDonald (1953) already recognized the cyclical nature of malaria as a product of the interaction of factors intrinsic to human hosts (e.g., immunity buildup) and exogenous to human beings, such as climatic seasonality, as well as the effects of changes in the environment that bring about the modification of the ecology of mosquitoes and their interaction with hu-

TABLE 2

Setting a research agenda: topics for malaria research in a changing environment

Field	**Current observations**	**Tools/Concepts**	**Key questions/Goals**
Ecological entomology	Rainfall and temperature • Pulses in rainfall can sometimes favor vector populations (e.g., Koenraadt et al. 2006), but this is not always the case (e.g., Chase and Knight 2003). • Temperature increase reduces the developmental time of mosquitoes (e.g., Bayoh and Lindsay 2003) • Differences in adult heat tolerance by mosquito species (e.g., Kirby and Lindsay 2004) • Density-dependence and mosquito population regulation is not fully understood (Yang et al. 2008).	• Classical population and community ecology: laboratory and field studies on oviposition/larval habitat selection (e.g., Huang et al. 2005), predation (e.g., Fillinger et al. 2009), and intra- (e.g., Gimnig et al. 2002) and interspecific competition (e.g., Kirby & Lindsay 2009; Paaijmans et al. 2009) using weather stations/sensors • Rainfall simulators to study aquatic vector ecology (Koenraadt and Harrington 2008) • Models for density dependence on adult and pre-imaginal stages (Rodriguez 1988)	• What types of landscape are conducive for increased mosquito productivity with changes in rainfall seasonality? • Is mosquito habitat selection influenced by the potential for autonomization from a changing environment (Janisch 1932)? • How important are changes in mosquito phenology for malaria transmission? What is the role of density dependence versus climatic factors herein?
	Landscape and vegetation • Mosquitoes feed on different sources of nectar, in flowers from different plant species (Yuval 1992). • Landscape affects presence of habitats and abundance of mosquito larvae (Fillinger et al. 2004, 2009; Minakawa et al. 2002b).	• Gas chromatography for nectar source identification (e.g., Manda et al. 2007b) • Field and laboratory sugar feeding studies (e.g., Manda et al. 2007a) • Topographic modeling of landscape to understand microclimatic differences (e.g., Cohen et al. 2008) • Remote sensing and Geographic Information Systems (e.g., Hay et al. 1998)	• Are mosquito and parasite fitness affected by nectar source? • Can the vegetation composition around a household be manipulated to control malaria? • Can remote sensing and geographical information systems be used to predict the presence of (productive) larval habitats?

continued

TABLE 2
Continued

Field	**Current observations**	**Tools/Concepts**	**Key questions/Goals**
	Mosquito surveillance ● Mosquitoes are difficult to capture in highland areas due to extremely low densities (Koenraadt et al. 2006). ● Mosquito larval habitats are dynamic (Minakawa et al. 2002b; Fillinger et al. 2004).	● Standardized collection methods across environmental gradients with more sensitive traps, to maximize diversity and probability of capture (e.g., Njiru et al. 2006; Qiu et al. 2007; Odiere et al. 2007) ● Metapopulation and source-sink ecology (Pulliam 1988)	● Can control efforts be targeted to key habitats? ● Can temporary habitats be managed? ● Can we use mathematical models to explain changes in the entomological inoculation rate associated with mosquito metapopulation dynamics driven by habitat abundance?
Neglected phenomena	Biological interventions ● Biological control remains a largely underexplored alternative to using insecticides for larval and adult control. In some instances, it has been successful when utilized (Yasuoka and Levins 2007a; Scholte et al. 2005). ● Misuse of insecticides and drugs can render them useless (Shanks et al. 2005). ● The use and implementation of successful control strategies (e.g., bednets and drugs) is often limited by strategies that follow industrialized models of trading. The poorest of the poor retain a high risk of malaria infection because of their lack of access to basic resources to stop malaria transmission (e.g., Mathanga and Bowie 2007).	● Community-based, ecologically sound, and biodiversity-friendly control strategies (Yasuoka et al. 2006a,b) ● Health impact assessments (Birley 1985): benefits of developmental strategies (e.g., dams, agriculture) can be outweighed by the exacerbation or emergence of disease transmission. ● Surveys on knowledge, attitudes, and practices to assess the understanding of malaria biology by affected communities, and to understand how decisions are made in regard to choices for treatment or bednet use (e.g., Yasuoka et al. 2006a,b) ● More research on the use of social marketing and traditional trading strategies for drug and bednet distribution (e.g., Mathanga and Bowie 2007)	● Goal: Sustainable, long-term control of malaria using biological control strategies. Need for more funding and research ● Knowledge intensive agriculture: vector and pest management are based on a robust knowledge of biological interactions, as opposed to the indiscriminate use of chemical inputs whose long-term environmental costs may be much higher than current benefits. ● Why do people misuse drugs and insecticides? How does (in)accurate knowledge modify practices to protect the individual/community from malaria transmission?

continued

TABLE 2
Continued

Field	**Current observations**	**Tools/Concepts**	**Key questions/Goals**
	Social factors		
	● All malaria transmission is local (Spielman 2006). Large scale patterns for other vector-borne diseases are determined by levels of social exclusion, with large differences across populations determined by the heterogeneity of the natural environment (Chaves et al. 2008b).	● Principles of social epidemiology (Cohen et al. 2007): populations stratified by income or access to resources; inclusion of socioeconomic variables in risk studies. ● The unequal ecological exchange (Jorgenson 2006): environmental costs and disease risks are canalized into less developed countries.	● At what spatial scale (i.e., local, regional, global) are social factors relevant in determining malaria risk? ● How to incorporate health and environmental costs and ecosystem services into global trade?
Evolutionary ecology	Drug resistance		
	● Drug resistance could have evolved during the shift toward endemic malaria transmission in the African highlands (e.g., Carter and Mendis 2002).	● Quantitative genetics modeling approach for converging evolutionary and ecological dynamics (Hairston et al. 2005; Khibnik and Kondrashov 1997)	● Is drug resistance a driver for malaria range expansion? How can the risk of selection for drug resistance be minimized?
	Vector Fitness		
	● Larger mosquitoes are more fecund, and smaller mosquitoes require more bloodmeals to complete a gonotrophic cycle (Lyimo and Takken 1993). ● When food deprived, larger non malaria vectors emerge following the application of control agents (Wilson et al. 1990) ● Intermediate mosquito body size maximizes parasite fitness under controlled environmental conditions (Lyimo and Koella 1992). ● Oviposition choices can impact non-malaria mosquito fitness (e.g., Ellis 2008).	● Life history theory for trade-offs (Stearns 2000): faster development-shorter size, longer development-larger size ● Metabolic theory (Brown et al. 2004) and physiological ecology (Briegel 2003): gonotrophic discordance as an evolutionary strategy; mosquito population dynamics and vectorial capacity affected by metabolic processes ● Mosquito oviposition studies at multiple spatial scales (e.g., Chaves et al, 2009). Ideal free distribution as a null hypothesis: no average fitness differences across heterogeneous landscapes (Ellis 2008)	● What are the evolutionary effects of warming trends on the life history of parasites and vectors? ● Does larviciding select for more efficient vectors? ● What are the effects of gonotrophic discordance on mosquito fitness and vectorial capacity? What are the trade-offs? ● Are mosquito oviposition choices finely or coarsely grained? Does larval habitat heterogeneity map into phenotypically different vectors?

continued

TABLE 2
Continued

Field	**Current observations**	**Tools/Concepts**	**Key questions/Goals**
	Vector Longevity		
	• Mortality is age dependent in non-malaria mosquitoes (Harrington et al. 2008; Styer et al. 2007).	• Vectorial capacity concept assumes that mosquito mortality is constant (Garret-Jones 1964)	• How does senescence (i.e., the increase of mortality with age) affect vectorial capacity?
	Ecological interactions		
	• Competition among sibling species and molecular chromosomal forms of the main malaria vector (An. gambiae) (Diabate et al. 2005; Koenraadt et al. 2004b; Koenraadt and Takken 2003) • Oviposition and larval habitat selection by An. gambiae is influenced by presence of conspecifics (Munga et al. 2006) • Indirect effects of predator presence in larval habitat selection by molecular forms of An. gambiae (Diabate et al. 2008) • Predation perception and resource abundance can modify phenotypic and life cycle traits of non-malaria mosquitoes (Beketov and Liess 2007).	• Chromosome banding; nuclear, ribosomal, and microsatellite molecular markers (Krzywinski and Besansky 2003) • Transplantation experiments (Diabate et al. 2008): removing larvae from original habitats to those that they do not colonize • Feedback loops (Levins and Schultz 1996): mosquito density can increase if their predators are more affected by warmer temperatures than their foraging resources. • Theory for indirect effects and trait-mediated interactions on foodweb, disruption of ecological interactions (Werner and Peacor 2003): resource rich larval habitats may produce less and smaller mosquitoes because of predator presence.	• How does competition during the aquatic life stage affect vectorial capacity? • Which vectors will invade/establish in areas that undergo environmental change? • How will climate change impact mosquito resources and/or their predators? • Can biological control reduce vectorial capacity? • What is the impact of climate change on the biological interactions involving mosquitoes?

mans. Demographic drivers, housing, and land use changes seem to be the most robustly linked to patterns of malaria transmission.

DEMOGRAPHIC DRIVERS

Human migration in the context of malaria transmission has been widely studied (Longstreth and Kondrachine 2002; Martens and Hall 2000; Prothero 1965; Sevilla-Casas 1993), and, in the case of the African highlands, it is well-known that the invasion of these regions by malarial parasites has been associated with the migration of people from the lowlands to the highlands (Lindsay and Martens 1998; Shanks et al. 2000; Shanks et al. 2005). The phenomenon of human migration is tightly linked to socioeconomic inequity and poverty (Martens and Hall 2000), the development of market-based agriculture, and land tenure inequity (Celli 1977; Humphreys 2001; Prothero 1965). Although malaria is becoming a major problem in urban areas today (Matthys et al. 2006a,b; Sattler et al. 2005), it is, as it has traditionally been, mostly a rural disease affecting people living and working in agricultural areas (Celli 1977; Ernst et al. 2006; Kitron 1987; Wilson 2003;

Yasuoka and Levins 2007b; Yasuoka et al. 2006a; Yasuoka et al. 2006b). As clearly presented by Prothero (1965), the commodification of agriculture in Africa led to a pattern of seasonal movement among landless farmers, migrating in order to work in commercially oriented estates, and this, subsequently, allowed for the invasion of parasites in new ecosystems where most of the native population were not immune to malaria infections. The latter is probably a global pattern, since the same patterns have been seen in Colombia (Sevilla-Casas 1993) and Afghanistan (Rab et al. 2003) as well. However, migrations can have the opposite effect, as exemplified by the cases of Venezuela and the USA, where urbanization and improved conditions for living have been associated with major declines in malaria (Chaves 2007; Humphreys 2001). Other demographic factors include population growth, the collapse of health services and vector control measures (Carter and Mendis 2002; Hay et al. 2002b; Lindsay and Martens 1998), and the deficient nutritional status of economically impoverished populations (Kiszewski and Teklehaimanot 2004).

HOUSING

Haddow (1942) and Garnham (1948) have already noted that the greater the number of people occupying a house, the more mosquitoes will be attracted into that house. By contrast, the design of houses may reduce the degree of exposure to blood-seeking mosquitoes, as simple construction may act as a physical barrier to prevent mosquitoes from entering (Lindsay et al. 2002). Houses with open eaves, mud rather than stone walls, and thatched roofing, as well as those occupied by a greater number of people and those without ceilings or cooking fires, were all associated with increased vector densities (Adiamah et al. 1993; Lindblade et al. 2000; Lindsay et al. 1995; Palsson et al. 2004; Zhou et al. 2007). The apparent increase in the number of mosquito bites also had an effect on morbidity levels, since such housing conditions were associated with increased morbidity (Adiamah et al. 1993; Ghebreyesus et al. 2000; Koram et al. 1995; Ong'echa et al. 2006; Somi et al. 2007; Ye et al. 2006). In contrast, Mbogo et al. (1999) found no difference in vector abundance between houses where children suffered from severe malaria and their control houses, while some housing factors, such as more than six occupants and the absence of a second bedroom, were associated with an increased risk. Other studies did not document any connection between house construction or household size and malaria morbidity (Luckner et al. 1998; Snow et al. 1998).

LAND USE CHANGE (AGRICULTURE AND DEFORESTATION)

Landscape transformations can lead to major changes in the functioning of ecosystems and their resilience or ability to cope with changes (Holling 1973). This has been shown in several cases for malaria. For example, Lindblade et al. (2000) showed that differences in temperature between forested and transformed landscapes (primarily for agriculture) at the same altitude in East Africa had major effects on mean temperature values, as well as temperature variability. Such differences are well-known to affect the ecology of malaria vectors in these regions; more specifically, these differences have been proven to affect the survival and gonotrophic cycle of vectors (Afrane et al. 2005; Afrane et al. 2006). In some cases, the difference in temperature can far surpass the increase of 0.5 °C attributable to climate change in the last sixty years (Pascual et al. 2006).

Growing and harvesting crops, either for self-subsistance or for monetary income, is the main economic activity in rural Africa. Besides their importance as a food source, crops may provide suitable micro-habitats for adult mosquitoes. Some crops also need regular irrigation, thereby creating aquatic habitats for the larval stages of malaria vectors. Ever since their introduction, rice irrigation schemes have been associated with a high malaria incidence in these agricultural communities (Grainger 1947). In many areas across Africa, irrigation seems to increase vector densities; however, the level of transmission may increase, remain unchanged, or even decrease (Ghebreyesus et al. 2000; Githeko et al. 1993; Ijumba et al. 2002;

Klinkenberg et al. 2005; Lindblade et al. 2000; Muturi et al. 2008; Okoye et al. 2005). In their review, Ijumba and Lindsay (2001) concluded that irrigation schemes in Africa do not seem to increase malaria risk in areas of stable transmission. Moreover, malaria risk may be reduced in communities with irrigation schemes as a result of species displacement (i.e., the opportunistic *An. arabiensis* thrives better in rice fields than the highly anthropophilic *An. funestus*) and greater wealth in these communities—a phenomenon known as the "paddies paradox." By contrast, in areas of unstable transmission, irrigation may aggravate the malaria situation. De Plaen et al. (2003) argued that, next to biological changes resulting from irrigation practices, socioeconomic transformations and gender repositioning are important mediators of change in malaria risk. The practice of intermittent irrigation significantly reduces vector populations, although fields should be drained completely, since the remaining pools and puddles may provide ideal sites for mosquito breeding (Klinkenberg et al. 2003). The effects of intermittent irrigation on clinical manifestations of malaria remain largely unknown (Keiser et al. 2005; Keiser et al. 2002) and, therefore, should be investigated in the future.

The invasion of malaria in the Bure highlands of Ethiopia (Kebede et al. 2005) was likely mediated by an increase in the fitness of *Anopheles arabiensis*—the mosquito vector present in the area—that resulted from its feeding on maize pollen after this crop was introduced to the area (Ye-Ebiyo et al. 2003; Ye-Ebiyo et al. 2000). However, this pattern was very localized, which led to the question of why it was not a problem in other places where maize had been introduced. But crops are not the only factors that can affect mosquito ecology and malaria transmission; other farming practices can lead to the exacerbation of malaria transmission as well. For example, the introduction of fish ponds has been associated with the establishment of *An. funestus*—a species whose ecology is associated with large ponds that can ultimately lengthen the transmission season—in areas where the species was never present before (Lockhart et al. 1969). The effects of agriculture on mosquito ecology and the transmission of malaria seem to be wider than commonly acknowledged. In a recent review, Yasuoka and Levins (2007b) presented the variety of effects that both deforestation and shifting agricultural practices have had on the ecology of mosquitoes vectoring malaria, finding a positive association between practices that promote the presence of water pools with access to light. Their work also showed how major landscape changes for the cultivation of agricultural crops—from coffee and cacao to rice, maize, and cassava—have always been associated with increased densities of mosquitoes and malaria outbreaks. Therefore, the links between agriculture and malaria are probably the most robust and the ones deserving more detailed research.

Agricultural practices related to the herding and farming of animals also impact malaria through the alteration of the community of hosts that could potentially serve as blood-feeding sources for mosquitoes. The presence of alternative hosts on the abundance of malaria vectors, and hence the risk of malaria, has received much attention, since the use of animals to divert host-seeking mosquitoes away from humans has been suggested as a measure to control malaria (zooprophylaxis) (WHO 1982). In many African settings, the presence of animals did not affect vector densities, entomological inoculation rates, or morbidity levels (Bøgh et al. 2001; Lindblade et al. 2000; Minakawa et al. 2002a; Snow et al. 1998). Moreover, in Gambia and Ethiopia, the malaria risk was greater in households that had many animals in or around their house (Adiamah et al. 1993; Deressa et al. 2007; Ghebreyesus et al. 2000). In a study on the coast of Kenya, the presence of more than two sheep was associated with an increased risk of severe malaria, while the presence of more than one dog was associated with a decreased risk (Mbogo et al. 1999). It can be concluded that, in the worst case scenario, the presence of animals provides an additional risk of malaria and surely does not divert host-seeking mosquitoes away from people vulnerable to the disease, although this may depend on the composition of the local sibling species (Mahande et al. 2007). However, it should also be mentioned that in some settings outside Africa, the presence of domestic animals does have a protective effect (Charlwood 2001).

The interaction between agriculture and malaria has also produced other patterns worthy of detailed study, specifically concerning how the disease can interfere with strategies for social development. The best documented study on this issue is historical and deals with inequity in land tenure in the Agro Romano, Italy (Celli 1977). Endemic malaria in this region led to the continuous abandonment or selling of land by small farmers, promoting the development of latifundia, or concentration of land with few owners. The latter occurred following numerous land redistribution reforms by different governments throughout the history of the Agro Romano, from classical times to the 20th century. Only after malaria was eradicated did latifundia and chronic poverty became a thing of the past in the Roman countryside (Celli 1977; Najera 1994). This pattern has been found in other places, as illustrated by a positive association between latifundia and malaria endemism in Spain (Beauchamp 1988) and the southeastern United States (Humphreys 2001) in the 1930s. This pattern also seems to be a global one, since malaria became endemic in several regions of the world only after these places experienced major deforestation in the name of economic development. Among these regions are the archipelago of the Mascareignes (modern day Mauritius and Reunion) (Julvez et al. 1990), São Tomé and Principe (Baptista 1996), and the Amazonic region of Peru (Vittor et al. 2006).

Thus, studies of land tenure dynamics and the effects of the historical disturbances that promoted its inequity (such as colonialism [Phombeah 2005]) can inform efforts to control malaria, and can also encourage its control as a way of promoting social change in zones where the disease is a burden (Celli 1977). This fact is further reinforced if the problem is viewed from a broader perspective and attention is given to conservation of forests and their associated biodiversity. As previously mentioned, deforestation alters landscape quality, which is of fundamental importance for biodiversity conservation. Deforestation diminishes the dispersal ability of species, thus increasing their extinction risk (Perfecto and Vandermeer 2008). It has been shown that large scale latifundia and disparity in land property size (Fearnside 1993), large external debts (Bawa and Dayanandan 1997), and precarious conditions for human social development (Jha and Bawa 2006), as well as unequal ecological exchange where more developed countries externalize their consumption-based environmental costs to less developed countries, thereby resulting in the environmental degradation of the latter (Jorgenson 2006), are some of the important underlying causes of deforestation. In general, the primary outcome of deforestation in terms of malaria transmission is an increase in its risk (de Castro et al. 2006; Guerra et al. 2006; Vittor et al. 2006). Therefore, understanding the effects of deforestation on malaria transmission will necessarily reveal that this is a problem whose roots are not in the nature of biological interactions across species, but rather in the implementation of models for social development and economic growth, as already shown for other vector-borne diseases (Chaves et al. 2008a). Table 2 presents directions for future research into the neglected aspects of malaria transmission.

Evolutionary Change at Different Time Scales

Ivan I. Schmalhausen (1949), in his fascinating but largely unnoticed work on evolution, clearly implied that organisms coping with changes in their environment become more vulnerable to small changes when pushed towards the limits of tolerance in any dimension of their existence (Schmalhausen 1949). This simple realization, which has been called Schmalhausen's law (Awerbuch et al. 2002; Chaves et al. 2008a,b), has major implications for all of ecology since it embodies the underlying evolutionary nature of the major ecological patterns seen in nature. It predicts that with a changing climate, changes in the dynamics of malaria (or any other biological phenomena) are to be expected in geographical regions at the edge of the distribution of the disease (or, more generally, a species). This fact is so universal that even early malaria studies by Macdonald (1953) realized that climatic variation has its largest effects on "the margins of the distribution of malaria whether in tropical or cooler zones" (p. 882). Today, major changes are being seen in the dynamics of malaria in the highlands of East Africa—a zone within the margins of what used to be the distribution of malaria (Lindsay and Birley 2004; Lindsay and Birley 1996; Lindsay and Martens 1998). As we discussed earlier, a multidimensional array of underlying factors is likely to be at play here, most of which may be sensitive to climatic change, whereas others may be undergoing evolutionary change. The three biological entities involved in malaria—humans, mosquitoes, and parasites—are very different, as are their effects on ecosystems, and possibly the way in which they can be affected by global climate change as well. The pressures imposed by such change can display evolutionary outcomes at different time scales and can have effects at levels ranging from the genetic to the cultural and social.

The effects of malaria on the population genetics of humans are well-known, dating back to the founders of population genetics (Haldane 1949) and biological anthropology (Livingstone 1958). These effects are mainly shown by the maintenance of deleterious alleles associated with advantages in coping with malaria, with the classical example being the heterozygote advantage for the sickle-cell anemia allele (Lewontin 1974). Since evolutionary change is known to occur as a function of the number of generations under natural selection or neutral evolution, it is likely that climate change will have little immediate effect on the ways in which humans evolve genetic means of defense, as the human pattern of evolution is generally associated with long-term agricultural practices (Odling-Smee et al. 2003). However, this may not be the case for mosquitoes and parasites, where developmental—and therefore generational—times are known to be reduced with rising temperatures (Pascual et al. 2006; Patz and Olson 2006), thereby increasing the likelihood of evolutionary changes in these two biological components of malaria as compared to the possibility of these changes in humans (using a common time scale). Such effects of natural selection have already been seen in the development of insecticide and drug resistance in mosquitoes and parasites, respectively (Carter and Mendis 2002; Shanks et al. 2005). The odds for neutral evolution (i.e., random genetic drift) are also likely to be increased, because an increased environmental variability is known to reduce the effective population size (Mueller and Joshi 2000), thus resulting in a greater level of uncertainty about the direction of any evolutionary change.

Schmalhausen's law also emphasizes the inherent multidimensional nature of all biological phenomena, but little attention has been given to other aspects of the biology of malaria. For example, predators and competitors can impact the distribution and abundance of mosquitoes (Blaustein and Chase 2007; Chase and Knight 2003; Knight et al. 2004), and, as argued before, these organisms can also evolve or even co-evolve, as evolutionary changes can happen at shorter temporal scales than commonly recognized among interacting populations. Table 2 presents directions for future research in the evolutionary ecology of malaria.

Schmalhausen's Law and Diseases in Changing Environments

The multidimensionality of malaria also calls for the realization that human biology is a socialized biology (Levins 1995). As we discussed earlier, a major underlying force in the spread of malaria, and even in the genetic structure of human populations, has been agriculture—a unique feature of the human species, deeply entangled with malaria historical dynamics in societies. For malaria, examples supporting its socialized nature are abundant: children of the poorest households are more likely to suffer malaria (Clarke et al. 2001); malaria transmission risk is reduced by a factor of 25 in countries with good health services (e.g., those able to provide prompt treatment) (Bouma 2003); educated communities are better at managing malaria risk factors, especially by reducing mosquito sources without compromising agricultural productivity (Yasuoka et al. 2006b); and only when robust structures of socioeconomic development have been present has malaria control been effective in the long run (Celli 1977; Kitron 1987; Lindsay and Birley 2004). Thus, only the integration of knowledge from the various fields discussed in this paper will provide new insights into the biology of malaria. To that end, Schmalhausen's law provides a conceptual framework within which the importance of different factors for malaria risk is evaluated at different spatial and temporal scales. The sensitivity to each factor at each scale can then be assessed, and interventions can be planned and coordinated in such a way that global, regional, and local scale actions are in concert, and opposing effects from a given driver can be understood as part of the same whole. With this framework, expectations regarding the time scales at which results are to be evaluated will be well–defined, and the goals of malaria eradication or sustained suppression will be more likely to be achieved (Feachem and Sabot 2008; Spielman et al. 1993).

Finally, global warming plays a major role in the collapse of ecosystems as functioning wholes (Collier and Webb 2002; Scheffer et al. 2001). However, areas where non-climatic factors have eliminated or controlled malaria are likely, *ceteris paribus* (i.e., everything else being equal), to be insensitive to the effects of global warming on disease transmission by vectors, while other areas where malaria is not present because of climatic conditions (e.g., cities in the highlands of the developing world, especially in Africa) are at potential risk of having an increased burden of the disease if no concerted action is put forward to stop global warming. In addition, the socialized biology of humans reveals that efforts to cope with malaria in a changing environment that is defined beyond scenarios of global warming should be aimed at promoting socioeconomic changes in the already disease-stricken populations around the world. Schmalhausen's law predicts that better conditions in people's lives can compensate for the effects of changes in other elements of the environment that may cause disease transmission to occur.

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REFERENCES

Abeku T. A., De Vlas S. J., Boorsboom G. J. J. M., Tadege A., Gebreyesus Y., Gebreyohannes H., Alamirew D., Seifu A., Nagelkerke N. J. D., Habbema J. D. F. 2004. Effects of meteorological factors on epidemic malaria in Ethiopia: a statistical modelling approach based on theoretical reasoning. *Parasitology* 128:585–593.

Adiamah J. H., Koram K. A., Thomson M. C., Lindsay S. W., Todd J., Greenwood B. M. 1993. Entomological risk factors for severe malaria in a peri-urban area of The Gambia. *Annals of Tropical Medicine and Parasitology* 87(5):491–500.

Afrane Y. A., Lawson B. W., Githeko A. K., Yan G. Y. 2005. Effects of microclimatic changes caused by land use and land cover on duration of gonotrophic cycles of *Anopheles gambiae* (Diptera: Culicidae) in western Kenya highlands. *Journal of Medical Entomology* 42(6):974–980.

Afrane Y. A., Zhou G. F., Lawson B. W., Githeko A. K., Yan G. Y. 2006. Effects of microclimatic changes caused by deforestation on the survivorship and reproductive fitness of *Anopheles gambiae* in Western Kenya highlands. *American Journal of Tropical Medicine and Hygiene* 74(5):772–778.

Andrewartha H. G. 1957. The use of conceptual models in population ecology. *Cold Spring Harbor Symposium in Quantitative Biology* 22:219–236.

Anthony R. L., Bangs M. J., Hamzah N., Purnomo H. B., Subianto B. 1992. Heightened transmission of stable malaria in an isolated population in the highlands of Irian Jaya, Indonesia. *American Journal of Tropical Medicine and Hygiene* 47(3):346–356.

Awerbuch T., Kiszewski A. E., Levins R. 2002. Surprise, nonlinearity and complex behaviour. Pages 96–119 in *Environmental Change, Climate and Health: Issues and Research Methods,* edited by P. Martens and A. J. McMichael. Cambridge (UK): Cambridge University Press.

Bangs M. J., Subianto D. B. 1999. El Niño and associated outbreaks of severe malaria in highland populations in Irian Jaya, Indonesia: a review and epidemiological perspective. *Southeast Asian Jour-*

nal of Tropical Medicine and Public Health 30(4): 608–619.

Baptista J. L. 1996. Subsidio para a história do paludismo em S. Tomé. *Acta Medica Portuguesa* 9:259–265.

Bawa K. S., Dayanandan S. 1997. Socioeconomic factors and tropical deforestation. *Nature* 386:562–563.

Bayoh M. N., Lindsay S. W. 2003. Effect of temperature on the development of the aquatic stages of *Anopheles gambiae* sensu stricto (Diptera: Culicidae). *Bulletin of Entomological Research* 93:375–381.

Beauchamp C. 1988. Fièvres d'hier, paludisme d'aujourd'hui: vie et mort d'une maladie. *Annales ESC* 43:249–275.

Beier J. C., Killeen G. F., Githure J. I. 1999. Short report: entomologic inoculation rates and *Plasmodium falciparum* malaria prevalence in Africa. *American Journal of Tropical Medicine and Hygiene* 61(1): 109–113.

Beketov M. A., Liess M. 2007. Predation risk perception and food scarcity induce alterations of life-cycle traits of the mosquito *Culex pipiens*. *Ecological Entomology* 32:405–410.

Binka F. N., Morris S. S., Ross D. A., Arthur P., Aryeetey M. E. 1994. Patterns of malaria morbidity and mortality in children in northern Ghana. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 88(4):381–385.

Birch L. C. 1957. The role of weather in determining the distribution and abundance of animals. *Cold Spring Harbor Symposium in Quantitative Biology* 22: 203–218.

Birley M. H. 1985. Forecasting the vector-borne disease implications of water development. *Parasitology Today* 1:34–36.

Blaustein L., Chase J. M. 2007. Interactions between mosquito larvae and species that share the same trophic level. *Annual Review Entomology* 52:489–507.

Bøgh C., Clarke S. E., Pinder M., Sanyang F., Lindsay S. W. 2001. Effect of passive zooprophylaxis on malaria transmission in the Gambia. *Journal of Medical Entomology* 38(6):822–828.

Bøgh C., Lindsay S. W., Clarke S. E., Dean A., Jawara M., Pinder M., Thomas C. J. 2007. High spatial resolution mapping of malaria transmission risk in The Gambia, West Africa, using LANDSAT TM satellite imagery. *American Journal of Tropical Medicine and Hygiene* 76(5):875–881.

Bouma M. J. 2003. Methodological problems and amendments to demonstrate effects of temperature on the epidemiology of malaria. A new perspective on the highland epidemics in Madagascar, 1972–1989. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 97(2):133–139.

Bouma M. J., Dye C., van der Kaay H. J. 1996. Falciparum malaria and climate change in the northwest frontier province of Pakistan. *American Journal of Tropical Medicine and Hygiene* 55(2):131–137.

Briegel H. 2003. Physiological bases of mosquito ecology. *Journal of Vector Ecology* 28(1):1–11.

Brockwell P. J., Davis R. A. 2002. *Introduction to Time Series and Forecasting*. Second Edition. New York: Springer.

Brown J. H., Gillooly J. F., Allen A. P., Savage V. M., West G. B. 2004. Toward a metabolic theory of ecology. *Ecology* 85(7):1771–1789.

Bryan J. H., Foley D. H., Sutherst R. W. 1996. Malaria transmission and climate change in Autralia. *Medical Journal of Australia* 164(6):345–347.

Carter R., Mendis K. N. 2002. Evolutionary and historical aspects of the burden of malaria. *Clinical Microbiology Reviews* 15(4):564–594.

Celli A. 1977. *The History of Malaria in the Roman Campagna from Ancient Times*. New York: AMS Press.

Charlwood D. 2001. Zooprophylaxis: are we in Plato's cave? *Trends in Parasitology* 17(11):517.

Chase J. M., Knight T. M. 2003. Drought-induced mosquito outbreaks in wetlands. *Ecology Letters* 6(11):1017–1024.

Chaves L. F. 2007. Casas Muertas and Oficina No. 1: internal migrations and malaria trends in Venezuela 1905–1945. *Parasitology Research* 101(1):19–23.

Chaves L. F., Cohen J. M., Pascual M., Wilson M. L. 2008a. Social exclusion modifies climate and deforestation impacts on a vector-borne disease. *Public Library of Science Neglected Tropical Diseases* 2(2): e176.

Chaves L. F., Kaneko A., Taleo G., Pascual M., Wilson M. L. 2008b. Malaria transmission pattern resilience to climatic variability is mediated by insecticide-treated nets. *Malaria Journal* 7:100.

Chaves L. F., Keogh C. L., Vazquez-Prokopec G. M., Kitron U. D. 2009. Combined sewage overflow enhances oviposition of *Culex quinquefasciatus* Say (Diptera: Culicidae) in urban areas. *Journal of Medical Entomology* 46(2):220–226.

Clarke S. E., Bøgh C., Brown R. C., Pinder M., Walraven G. E. L., Lindsay S. W. 2001. Do untreated bed nets protect against malaria? *Transactions of the Royal Society of Tropical Medicine and Hygiene* 95(5): 457–462.

Clarke S. E., Bøgh C., Brown R. C., Walraven G. E. L., Thomas C. J., Lindsay S. W. 2002. Risk of malaria attacks in Gambian children is greater away from malaria vector breeding sites. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 96(5): 499–506.

Clements A. N. 1999. *The Biology of Mosquitoes, Volume 2: Sensory Reception and Behaviour*. Wallingford (UK): CABI Publishing.

Cohen J. M., Ernst K. C., Lindblade K. A., Vulule J. M., John C. C., Wilson M. L. 2008. Topography-derived wetness indices are associated with household-level malaria risk in two communities in the western Kenyan highlands. *Malaria Journal* 7:40.

Cohen J. M., Wilson M. L., Aiello A. E. 2007. Analysis of social epidemiology research on infectious diseases: historical patterns and future opportunities. *Journal of Epidemiology and Community Health* 61(12):1021–1027.

Collier M., Webb R. H. 2002. *Floods, Droughts, and Climate Change*. Tucson (AZ): University of Arizona Press.

Coz J. 1973. Les mécanismes d'isolement génétique dans le complexe *Anopheles gambiae* Giles. *Cah ORSTOM ser Entomol méd Parasitol* 11:41–56.

Craig M. H., Kleinschmidt I., Nawn J. B., le Sueur D., Sharp B. L. 2004. Exploring 30 years of malaria case data in KwaZulu-Natal, South Africa: Part I. The impact of climatic factors. *Tropical Medicine and International Health* 9(12):1247–1257.

Craig M. H., Snow R. W., le Sueur D. 1999. A climate-based distribution model of malaria transmission in sub-Saharan Africa. *Parasitology Today* 15(3):105–111.

de Castro M. C., Monte-Mór R. L., Sawyer D. O., Singer B. H. 2006. Malaria risk on the Amazon frontier. *Proceedings of the National Academy of Sciences USA* 103(7):2452–2457.

della Torre A., Tu Z. J., Petrarca V. 2005. On the distribution and genetic differentiation of *Anopheles gambiae* s.s. molecular forms. *Insect Biochemistry and Molecular Biology* 35(7):755–769.

Delmont J. 1982. Paludisme et variations climatiques saisonnières en savane soudanienne d'Afrique de l'Ouest. *Cahiers d'Études Africaines* 22(85–86):117–133.

De Plaen R., Geneau R., Teuscher T., Koutoua A., Seka M. L. 2003. Living in the paddies: a social science perspective on how inland valley irrigated rice cultivation affects malaria in Northern Côte d'Ivoire. *Tropical Medicine & International Health* 8:459–470.

Deressa W., Ali A., Berhane Y. 2007. Household and socioeconomic factors associated with childhood febrile illnesses and treatment seeking behaviour in an area of epidemic malaria in rural Ethiopia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 101(9):939–947.

de Zulueta J. 1987. Changes in the geographical distribution of malaria throughout history. *Parassitologia* 29:193–205.

de Zulueta J. 1994. Malaria and ecosystems: from prehistory to posteradication. *Parassitologia* 36(1–2):7–15.

Diabate A., Dabire R., Heidenberger K., Crawford J., Lamp W. O., Culler L. E., Lehmann T. 2008. Evidence for divergent selection between the molecular forms of *Anopheles gambiae*: role of predation. *BMC Evolutionary Biology* 8:5.

Diabate A., Dabire R. K., Kim E. H., Dalton R., Millogo N., Baldet T., Simard F., Gimnig J. E., Hawley W. A., Lehmann T. 2005. Larval development of the molecular forms of *Anopheles gambiae* (Diptera: Culicidae) in different habitats: a transplantation experiment. *Journal of Medical Entomology* 42:548–553.

Drakeley C. J., Carneiro I., Reyburn H., Malima R., Lusingu J. P. A., Cox J., Theander T. G., Nkya W. M. M. M., Lemnge M. M., Riley E. M. 2005. Altitude-dependent and -independent variations in *Plasmodium falciparum* prevalence in northeastern Tanzania. *Journal of Infectious Diseases* 191(10):1589–1598.

Duncan K. 1993. The possible influence of climate on historical outbreaks of malaria in Scotland. *Proceedings of the Royal College of Physicians Edinburgh* 23(1):55–62.

Ellis A. M. 2008. Incorporating density dependence into the oviposition preference-offspring performance hypothesis. *Journal of Animal Ecology* 77(2):247–256.

Ernst K. C., Adoka S. O., Kowuor D. O., Wilson M. L., John C. C. 2006. Malaria hotspot areas in a highland Kenya site are consistent in epidemic and non-epidemic years and are associated with ecological factors. *Malaria Journal* 5:78.

Faraway J. J. 2005. *Linear Models with R*. Boca Raton (FL): CRC Press.

Feachem R., Sabot O. 2008. A new global malaria eradication strategy. *Lancet* 371(9624):1633–1635.

Fearnside P. M. 1993. Deforestation in Brazilian Amazonia: the effect of population and land tenure. *Ambio* 22:537–545.

Fillinger U., Sombroek H., Majambere S., van Loon E., Takken W., Lindsay S. W. 2009. Identifying the most productive breeding sites for malaria mosquitoes in The Gambia. *Malaria Journal* 8:62.

Fillinger U., Sonye G., Killeen G. F., Knols B. G. J., Becker N. 2004. The practical importance of permanent and semipermanent habitats for controlling aquatic stages of *Anopheles gambiae* sensu lato mosquitoes: operational observations from a rural town in western Kenya. *Tropical Medicine & International Health* 9(12):1274–1289.

Gagnon A. S., Smoyer-Tomic K. E., Bush A. B. G. 2002. The El Niño southern oscillation and malaria epidemics in South America. *International Journal of Biometeorology* 46(2):81–89.

Garnham P. C. C. 1929. Malaria in Kisumu, Kenya colony. *Journal of Tropical Medicine and Hygiene* 32:207–216.

Garnham P. C. C. 1948. The incidence of malaria at high altitudes. *Journal of the National Malaria Society* 7(4):275–284.

Garrett-Jones C. 1964. The human blood index of malaria vectors in relation to epidemiological assessment. *Bulletin of the World Health Organization* 30(2):241–261.

Ghebreyesus T. A., Haile M., Witten K. H., Getachew A., Yohannes M., Lindsay S. W., Byass P. 2000. Household risk factors for malaria among children in the Ethiopian highlands. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 94(1): 17–21.

Ghebreyesus T. A., Haile M., Witten K. H., Getachew A., Yohannes A. M., Yohannes M., Teklehaimanot H. D., Lindsay S. W., Byass P. 1999. Incidence of malaria among children living near dams in northern Ethiopia: community based incidence survey. *British Medical Journal* 319(7211):663–666.

Gill C. A. 1920. The relationship between malaria and rainfall. *Indian Journal of Medical Research* 37:618–632.

Gillies M. T., Coetzee M. 1987. A supplement to the anophelinae of Africa south of the Sahara. *Publications of the South African Institute for Medical Research* 55:79–86.

Gimnig J. E., Ombok M., Otieno S., Kaufman M. G., Vulule J. M., Walker E. D. 2002. Density-dependent development of *Anopheles gambiae* (Diptera: Culicidae) larvae in artificial habitats. *Journal of Medical Entomology* 39(1):162–172.

Githeko A. K., Ndegwa W. 2001. Predicting malaria epidemics in the Kenyan highlands using climate data: a tool for decision makers. *Global Change and Human Health* 2:54–63.

Githeko A. K., Service M. W., Mbogo C. M., Atieli F. K., Juma F. O. 1993. *Plasmodium falciparum* sporozoite and entomological inoculation rates at the Ahero rice irrigation scheme and the Miwani sugar-belt in western Kenya. *Annals of Tropical Medicine and Parasitology* 87:379–391.

Gomez-Elipe A., Otero A., van Herp M., Aguirre-Jaime A. 2007. Forecasting malaria incidence based on monthly case reports and environmental factors in Karuzi, Burundi, 1997-2003. *Malaria Journal* 6:129.

Grainger W. E. 1947. The experimental control of mosquito breeding in rice fields in Nyanza Province, Kenya, by intermittent irrigation and other methods. *East African Medical Journal* 24:16–22.

Guerra C. A., Snow R. W., Hay S. I. 2006. A global assessment of closed forests, deforestation and malaria risk. *Annals of Tropical Medicine and Parasitology* 100(3):189–204.

Haddow A. J. 1942. The mosquito fauna and climate of native huts at Kisumu, Kenya. *Bulletin of Entomological Research* 33:91–142.

Hairston N. G., Jr., Ellner S. P., Geber M. A., Yoshida T., Fox J. A. 2005. Rapid evolution and the convergence of ecological and evolutionary time. *Ecology Letters* 8:1114–1127.

Haldane J. B. S. 1949. Disease and evolution. *La Ricerca Scientifica* 19(supplement):68–76.

Harrington L. C., Vermeylen F., Jones J. J., Kitthawee S., Sithiprasasna R., Edman J. D., Scott T. W. 2008. Age-dependent survival of the dengue vector *Aedes aegypti* (Diptera: Culicidae) demonstrated by simultaneous release-recapture of different age cohorts. *Journal of Medical Entomology* 45(2):307–313.

Hay S. I., Cox J., Rogers D. J., Randolph S. E., Stern D. I., Shanks G. D., Myers M. F., Snow R. W. 2002a. Climate change and the resurgence of malaria in the East African highlands. *Nature* 415(6874):905–909.

Hay S. I., Myers M. F., Burke D. S., Vaughn D. W., Endy T., Ananda N., Shanks G. D., Snow R. W., Rogers D. J. 2000. Etiology of interepidemic periods of mosquito-borne disease. *Proceedings of the National Academy of Sciences USA* 97(16):9335–9339.

Hay S. I., Rogers D. J., Randolph S. E., Stern D. I., Cox J., Shanks G. D., Snow R. W. 2002b. Hot topic or hot air? Climate change and malaria resurgence in East African highlands. *Trends in Parasitology* 18(12):530–534.

Hay S. I., Shanks G. D., Stern D. I., Snow R. W., Randolph S. E., Rogers D. J. 2005. Climate variability and malaria epidemics in the highlands of East Africa. *Trends in Parasitology* 21(2):52–53.

Hay S. I., Snow R. W., Rogers D. J. 1998. Predicting malaria seasons in Kenya using multitemporal meteorological satellite sensor data. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 92(1): 12–20.

Hernandez M. J. 1998. Dynamics of transition between population interactions: a nonlinear interaction α-function defined. *Proceedings of the Royal Society of London, Series B: Biological Sciences* 265(1404): 1433–1440.

Holling C. S. 1973. Resilience and stability of ecological systems. *Annual Review of Ecology and Systematics* 4:1–23.

Holstein M. H. 1954. *Biology of* Anopheles gambiae: *Research in French West Africa*. Geneva (Switzerland): World Health Organization.

Hoshen M. B., Morse A. P. 2004. A weather-driven model of malaria transmission. *Malaria Journal* 3:32.

Huang J., Walker E. D., Giroux P. Y., Vulule J., Miller J. R. 2005. Ovipositional site selection by *Anopheles gambiae*: influences of substrate moisture and texture. *Medical and Veterinary Entomology* 19:442–450.

Humphreys M. 2001. *Malaria: Poverty, Race, and Public Health in the United States*. Baltimore (MD): Johns Hopkins University Press.

Ijumba J. N., Lindsay S. W. 2001. Impact of irrigation on malaria in Africa: paddies paradox. *Medical and Veterinary Entomology* 15(1):1–11.

Ijumba J. N., Mosha F. W., Lindsay S. W. 2002. Malaria transmission risk variations derived from different agricultural practices in an irrigated area of northern Tanzania. *Medical and Veterinary Entomology* 16(1):28–38.

Janisch E. 1932. The influence of temperature on the life history of insects. *Transactions of the Entomological Society of London* 80:137–168.

Jepson W. F., Moutia A., Courtois C. 1947. The malaria problem in Mauritius: the bionomics of Mauritian anophelines. *Bulletin of Entomological Research* 38:177–208.

Jha S., Bawa K. S. 2006. Population growth, human development, and deforestation in biodiversity hotspots. *Conservation Biology* 20(3):906–912.

Jones C. O. H., Williams H. A. 2004. The social burden of malaria: what are we measuring? *American Journal of Tropical Medicine and Hygiene* 71(2 supplement):156–161.

Jorgenson A. K. 2006. Unequal ecological exchange and environmental degradation: a theoretical proposition and cross-national study of deforestation, 1990-2000. *Rural Sociology* 71:685–712.

Julvez J., Mouchet J., Ragavoodoo C. 1990. Epidémiologie historique du paludisme dans l'archipel des Mascareignes (Ocean Indien). *Annales Société Belge de Médecine Tropicale* 70:249–262.

Kazembe L. N. 2007. Spatial modelling and risk factors of malaria incidence in northern Malawi. *Acta Tropica* 102(2):126–137.

Kebede A., McCann J. C., Ye-Ebiyo Y., Kiszewski A. E. 2005. New evidence of the effects of agro-ecologic change on malaria transmission. *American Journal of Tropical Medicine and Hygiene* 73(4):676–680.

Keiser J., De Castro M. C., Maltese M. F., Bos R., Tanner M., Singer B. H., Utzinger J. 2005. Effect of irrigation and large dams on the burden of malaria on a global and regional scale. *American Journal of Tropical Medicine and Hygiene* 72(4):392–406.

Keiser J., Utzinger J., Singer B. H. 2002. The potential of intermittent irrigation for increasing rice yields, lowering water consumption, reducing methane emissions, and controlling malaria in African rice fields. *Journal of the American Mosquito Control Association* 18(4):329–340.

Khibnik A. I., Kondrashov A. S. 1997. Three mechanisms of Red Queen dynamics. *Proceedings of the Royal Society of London, Series B: Biological Sciences* 264(1384):1049–1056.

Killeen G. F., Fillinger U., Kiche I., Gouagna L. C., Knols B. G. J. 2002. Eradication of *Anopheles gambiae* from Brazil: lessons for malaria control in Africa? *Lancet Infectious Diseases* 2(10):618–627.

Killian A. H. D., Langi P., Talisuna A., Kabagambe G. 1999. Rainfall pattern, El Niño and malaria in Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 93:22–23.

Kirby M. J., Lindsay S. W. 2004. Responses of adult mosquitoes of two sibling species, *Anopheles arabiensis* and *A. gambiae s.s.* (Diptera: Culicidae), to high temperatures. *Bulletin of Entomological Research* 94(5):441–448.

Kirby M. J., Lindsay S. W. 2009. Effect of temperature and inter-specific competition on the development and survival of *Anopheles gambiae* sensu stricto and *An. arabiensis* larvae. *Acta Tropica* 109(2):118–123.

Kiszewski A. E., Teklehaimanot A. 2004. A review of the clinical and epidemiologic burdens of epidemic malaria. *American Journal of Tropical Medicine and Hygiene* 71(supplement 2):128–135.

Kitron U. 1987. Malaria, agriculture, and development: lessons from past campaigns. *International Journal of Health Services* 17(2):295–326.

Kleinschmidt I., Sharp B. L., Clarke G. P. Y., Curtis B., Fraser C. 2001. Use of generalized linear mixed models in the spatial analysis of small-area malaria incidence rates in KwaZulu Natal, South Africa. *American Journal of Epidemiology* 153(12):1213–1221.

Klinkenberg E., McCall P. J., Hastings I. M., Wilson M. D., Amerasinghe F. P., Donnelly M. J. 2005. Malaria and irrigated crops, Accra, Ghana. *Emerging Infectious Diseases* 11(8):1290–1293.

Klinkenberg E., Takken W., Huibers F., Touré Y. T. 2003. The phenology of malaria mosquitoes in irrigated rice fields in Mali. *Acta Tropica* 85(1):71–82.

Knight T. M., Chase J. M., Goss C. W., Knight J. J. 2004. Effects of interspecific competition, predation, and their interaction on survival and development time of immature *Anopheles quadrimaculatus*. *Journal of Vector Ecol*ogy 29(2):277–284.

Koenraadt C. J. M., Githeko A. K., Takken W. 2004a. The effects of rainfall and evapotranspiration on the temporal dynamics of *Anopheles gambiae* s.s. and *Anopheles arabiensis* in a Kenyan village. *Acta Tropica* 90(2):141–153.

Koenraadt C. J. M., Harrington L. C. 2008. Flushing effect of rain on container-inhabiting mosquitoes *Aedes aegypti* and *Culex pipiens* (Diptera: Culicidae). *Journal of Medical Entomology* 45(1):28–35.

Koenraadt C. J. M., Majambere S., Hemerik L., Takken W. 2004b. The effects of food and space on the occurrence of cannibalism and predation among larvae of *Anopheles gambiae* sl. *Entomologia Experimentalis et Applicata* 112(2):125–134.

Koenraadt C. J. M., Paaijmans K. P., Schneider P., Githeko A. K., Takken W. 2006. Low larval vector survival explains unstable malaria in the western Kenya highlands. *Tropical Medicine & International Health* 11(8):1195–1205.

Koenraadt C. J. M., Takken W. 2003. Cannibalism and predation among larvae of the *Anopheles gambiae* complex. *Medical and Veterinary Entomology* 17(1): 61–66.

Koram K. A., Bennett S., Adiamah J. H., Greenwood B. M. 1995. Socio-economic risk factors for malaria in a peri-urban area of The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 89(2):146–150.

Kovats R. S., Bouma M. J., Hajat S., Worrall E., Haines A. 2003. El Niño and health. *Lancet* 362(9394): 1481–1489.

Krzywinski J., Besansky N. J. 2003. Molecular systematics of *Anopheles*: from subgenera to subpopulations. *Annual Review of Entomology* 48:111–139.

La Grange J. J. P. 1995. Survey of anopheline mosquitoes (Diptera: Culicidae) in a malarious area of Swaziland. *African Entomology* 3:217–219.

Lautze J., McCartney M., Kirshen P., Olana D., Jayasinghe G., Spielman A. 2007. Effect of a large dam on malaria risk: the Koka reservoir in Ethiopia. *Tropical Medicine & International Health* 12(8):982–989.

Levins R. 1966. The strategy of model building in population biology. *American Scientist* 54:421–431.

Levins R. 1995. Toward an integrated epidemiology. *Trends in Ecology and Evolution* 10(7):304.

Levins R. 2006. Strategies of abstraction. *Biology & Philosophy* 21(5):741–755.

Levins R., Schultz B. B. 1996. Effects of density dependence, feedback and environmental sensitivity on correlations among predators, prey and plant resources: models and practical implications. *Journal of Animal Ecology* 65(6):802–812.

Lewontin R. C. 1974. *The Genetic Basis of Evolutionary Change*. New York: Columbia University Press.

Lewontin R., Levins R. 2000. Let the numbers speak. *International Journal of Health Services* 30(4):873–877.

Lindblade K. A., Walker E. D., Onapa A. W., Katungu J., Wilson M. L. 1999. Highland malaria in Uganda: prospective analysis of an epidemic associated with El Niño. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 93(5):480–487.

Lindblade K. A., Walker E. D., Onapa A. W., Katungu J., Wilson M. L. 2000. Land use change alters malaria transmission parameters by modifying temperature in a highland area of Uganda. *Tropical Medicine & International Health* 5(4):263–274.

Lindsay S. W., Armstrong Schellenberg J. R., Zeiler H. A., Daly R. J., Salum F. M., Wilkins H. A. 1995. Exposure of Gambian children to *Anopheles gambiae* malaria vectors in an irrigated rice production area. *Medical and Veterinary Entomology* 9(1):50–58.

Lindsay S. W., Birley M. H. 1996. Climate change and malaria transmission. *Annals of Tropical Medicine and Parasitology* 90(6):573–588.

Lindsay S. W., Birley M. 2004. Rural development and malaria control in Sub-Saharan Africa. *Ecohealth* 1(2):129–137.

Lindsay S. W., Bødker R., Malima R., Msangeni H. A., Kisinza W. 2000. Effect of 1997–1998 El Niño on highland malaria in Tanzania. *Lancet* 355(9208): 989–990.

Lindsay S. W., Emerson P. M., Charlwood J. D. 2002. Reducing malaria by mosquito-proofing houses. *Trends in Parasitology* 18(11):510–514.

Lindsay S. W., Martens W. J. 1998. Malaria in the African highlands: past, present and future. *Bulletin of the World Health Organization* 76:33–45.

Livingstone F. B. 1958. Anthropological implications of sickle-cell gene distribution in West Africa. *American Anthropologist* 60:533–562.

Lockhart J. D. F., Highton R. B., McMahon J. P. 1969. Public health problems arising out of man-made fish ponds in the Western Province of Kenya. *East African Medical Journal* 46(8):471–480.

Longstreth J., Kondrachine A. 2002. Population migration and malaria. Pages 270–280 in *The Contextual Determinants of Malaria,* edited by E. Casman and H. Dowlatabadi. Washington (D.C.): Resources for the Future.

Luckner D., Lell B., Greve B., Lehman L. G., Schmidt-Ott R. J., Matousek P., Herbich K., Schmid D., Mba R., Kremsner P. G. 1998. No influence of socioeconomic factors on severe malarial anaemia, hyperparasitaemia or reinfection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 92(5):478–481.

Lyimo E. O., Koella J. C. 1992. Relationship between body size of adult *Anopheles gambiae* s.l. and infection with the malaria parasite *Plasmodium falciparum. Parasitology* 104:233–237.

Lyimo E. O., Takken W. 1993. Effects of adult body size on fecundity and the pre-gravid rate of *Anopheles gambiae* females in Tanzania. *Medical and Veterinary Entomology* 7(4):328–332.

Mabaso M. L. H., Kleinschmidt I., Sharp B. L., Smith T. 2007. El Niño Southern Oscillation (ENSO) and annual malaria incidence in Southern Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 101(4):326–330.

Macdonald G. 1953. The analysis of malaria epidemics. *Tropical Diseases Bulletin* 50(10):871–889.

Madhavan K. T., Jajoo U. N., Bhalla A. 2001. Seasonal variations in incidence of severe and complicated malaria in central India. *Indian Journal of Medical Sciences* 55(1):43–46.

Mahande A., Mosha F., Mahande J., Kweka E. 2007. Feeding and resting behaviour of malaria vector, *Anopheles arabiensis* with reference to zooprophylaxis. *Malaria Journal* 6:100.

Malakooti M. A., Biomndo K., Shanks G. D. 1998. Reemergence of epidemic malaria in the highlands of western Kenya. *Emerging Infectious Diseases* 4:671–676.

Manda H., Gouagna L. C., Foster W. A., Jackson R. R., Beier J. C., Githure J. I., Hassanali A. 2007a. Effect of discriminative plant-sugar feeding on the survival and fecundity of *Anopheles gambiae*. *Malaria Journal* 6:113.

Manda H., Gouagna L. C., Nyandat E., Kabir E. W., Jackson R. R., Foster W. A., Githure J. I., Beier J. C., Hassanali A. 2007b. Discriminative feeding behaviour of *Anopheles gambiae* s.s. on endemic plants in western Kenya. *Medical and Veterinary Entomology* 21(1):103–111.

Martens P., Hall L. 2000. Malaria on the move: human population movement and malaria transmission. *Emerging Infectious Diseases* 6(2):103–109.

Mathanga D. P., Bowie C. 2007. Malaria control in Malawi: are the poor being served? *International Journal for Equity in Health* 6:22.

Matthys B., N'Goran E. K., Koné M., Koudou B. G., Vounatsou P., Cissé G., Tschannen A. B., Tanner M., Utzinger J. 2006a. Urban agricultural land use and characterization of mosquito larval habitats in a medium-sized town of Côte d'Ivoire. *Journal of Vector Ecology* 31(2):319–333.

Matthys B., Vounatsou P., Raso G., Tschannen A. B., Becket E. G., Gosoniu L., Cissé G., Tanner M., N'Goran E. K., Utzinger J. 2006b. Urban farming and malaria risk factors in a medium-sized town in Côte d'Ivoire. *American Journal of Tropical Medicine and Hygiene* 75(6):1223–1231.

Mbogo C. N. M., Kabiru E. W., Glass G. E., Forster D., Snow R. W., Khamala C. P. M., Ouma J. H., Githure J. I., Marsh K., Beier J. C. 1999. Vector-related case-control study of severe malaria in Kilifi district, Kenya. *American Journal of Tropical Medicine and Hygiene* 60(5):781–785.

Minakawa N., Seda P., Yan G. 2002a. Influence of host and larval habitat distribution on the abundance of African malaria vectors in western Kenya. *American Journal of Tropical Medicine and Hygiene* 67:32–38.

Minakawa N., Sonye G., Mogi M., Githeko A., Yan G. 2002b. The effects of climatic factors on the distribution and abundance of malaria vectors in Kenya. *Journal of Medical Entomology* 39(6):833–841.

Minakawa N., Sonye G., Mogi M., Yan G. 2004. Habitat characteristics of *Anopheles gambiae* s.s. larvae in a Kenyan highland. *Medical and Veterinary Entomology* 18(3):301–305.

Mueller I., Namuigi P., Kundi J., Ivivi R., Tandrapah T., Bjorge S., Reeder J. C. 2005. Epidemic malaria in the highlands of Papua New Guinea. *American Journal of Tropical Medicine and Hygiene* 72(5):554–560.

Mueller L. D., Joshi A. 2000. *Stability in Model Populations*. Princeton (NJ): Princeton University Press.

Munga S., Minakawa N., Zhou G. F., Barrack O. A. J., Githeko A. K., Yan G. Y. 2006. Effects of larval competitors and predators on oviposition site selection of *Anopheles gambiae* sensu stricto. *Journal of Medical Entomology* 43(2):221–224.

Muturi E. J., Muriu S., Shililu J., Mwangangi J., Jacob B. G., Mbogo C., Githure J., Novak R. J. 2008. Effect of rice cultivation on malaria transmission in central Kenya. *American Journal of Tropical Medicine and Hygiene* 78(2):270–275.

Najera J. A. 1994. The control of tropical diseases and socioeconomic development (with special reference to malaria and its control). *Parassitologia* 36:17–33.

Ndiaye O., Le Hesran J. Y., Etard J. F., Diallo A., Simondon F., Ward M. N., Robert V. 2001. Variations climatiques et mortalité attribuée au paludisme dans la zone de Niakhar, Sénégal, de 1984 à 1996. *Cahiers d'études et de recherche francophones/Santé* 11:25–33.

Nicholson A. J. 1957. The self-adjustment of populations to change. *Cold Spring Harbor Symposium in Quantitative Biology* 22:153–173.

Njiru B. N., Mukabana W. R., Takken W., Knols B. G. J. 2006. Trapping of the malaria vector *Anopheles gambiae* with odour-baited MM-X traps in semi-field conditions in western Kenya. *Malaria Journal* 5:39.

Odiere M., Bayoh M. N., Gimnig J., Vulule J., Irungu L., Walker E. 2007. Sampling outdoor, resting *Anopheles gambiae* and other mosquitoes (Diptera: Culicidae) in western Kenya with clay pots. *Journal of Medical Entomology* 44:14–22.

Odling-Smee F. J., Laland K. N., Feldman M. W. 2003. *Niche Construction: The Neglected Process in Evolution*. Princeton (NJ): Princeton University Press.

Oesterholt M. J. A. M., Bousema J. T., Mwerinde O. K., Harris C., Lushino P., Masokoto A., Mwerinde H., Mosha F. W., Drakeley C. J. 2006. Spatial and temporal variation in malaria transmission in a low endemicity area in northern Tanzania. *Malaria Journal* 5:98.

Okoye P. N., Wilson M. D., Boakye D. A., Brown C. A. 2005. Impact of the Okyereko irrigation project in Ghana on the risk of human malaria infection by Anopheles species (Diptera: Culicidae). *African Entomology* 13(2):249–253.

Ong'echa J. M., Keller C. C., Were T., Ouma C., Otieno R. O., Landis-Lewis Z., Ochiel D., Slingluff J. L., Mogere S., Ogonji G. A., Orago A. S., Vulule J. M., Kaplan S. S., Day R. D., Perkins D. 2006. Parasitemia, anemia, and malarial anemia in infants and young children in a rural holoendemic *Plasmodium falciparum* transmission area. *American*

Journal of Tropical Medicine and Hygiene 74(3):376–385.

Onori E., Grab B. 1980. Indicators for the forecasting of malaria epidemics. *Bulletin of the World Health Organization* 58:91–98.

Paaijmans K. P., Huijben S., Githeko A. K, Takken W. 2009. Competitive interactions between larvae of the malaria mosquitoes *Anopheles arabiensis* and *Anopheles gambiae* under semi-field conditions in western Kenya. *Acta Tropica* 109(2):124–130.

Palsson K., Jaenson T. G. T., Dias F., Laugen A. T., Bjorkman A. 2004. Endophilic *Anopheles* mosquitoes in Guinea Bissau, West Africa, in relation to human housing conditions. *Journal of Medical Entomology* 41(4):746–752.

Pascual M., Ahumada J. A., Chaves L. F., Rodó X., Bouma M. 2006. Malaria resurgence in the east African highlands: temperature trends revisited. *Proceedings of the National Academy of Sciences USA* 103(15):5829–5834.

Pascual M., Bouma M. J. 2009. Do rising temperatures matter? *Ecology* 90(4):906–912.

Pascual M., Cazelles B., Bouma M. J., Chaves L. F., Koelle K. 2008. Shifting patterns: malaria dynamics and rainfall variability in an East African highland. *Proceedings of the Royal Society of London, Series B: Biological Sciences* 275(1631):123–132.

Patz J. A., Hulme M., Rosenzweig C., Mitchell T. D., Goldberg R. A., Githeko A. K., Lele S., McMichael A. J., LeSueur D. 2002. Regional warming and malaria resurgence. *Nature* 420:627–628.

Patz J. A., Olson S. H. 2006. Malaria risk and temperature: influences from global climate change and local land use practices. *Proceedings of the National Academy of Sciences USA* 103(15):5635–5636.

Patz J. A., Strzepek K., Lele S., Hedden M., Greene S., Noden B., Hay S. I., Kalkstein L., Beier J. C. 1998. Predicting key malaria transmission factors, biting and entomological inoculation rates, using modeled soil moisture in Kenya. *Tropical Medicine & International Health* 3(10):818–827.

Perfecto I., Vandermeer J. 2008. Biodiversity conservation in tropical agroecosystems: a new conservation paradigm. *Annals of the New York Academy of Sciences* 1134:173–200.

Petrarca V., Beier J. C., Onyango F., Koros J., Asiago C., Koech D. K., Roberts C. R. 1991. Species composition of the *Anopheles gambiae* complex (Diptera: Culicidae) at two sites in western Kenya. *Journal of Medical Entomology* 28(3):307–313.

Phombeah G. 2005. Kenya: overthrowing colonial landlords. *BBC Focus on Africa* 16:30–33.

Prothero R. M. 1965. *Migrants and Malaria.* London (UK): Longmans.

Pulliam H. R. 1988. Sources, sinks, and population regulation. *American Naturalist* 132:652–661.

Qiu Y. T., Smallegange R. C., Ter Braak C. J. F., Spitzen J., Van Loon J. J. A., Jawara M., Milligan P., Galimard A. M., Van Beek T. A., Knols B. G. J., Takken W. 2007. Attractiveness of MM-X traps baited with human or synthetic odor to mosquitoes (Diptera: Culicidae) in the Gambia. *Journal of Medical Entomology* 44(6):970–983.

Rab M. A., Freeman T. W., Rahim S., Durrani N., Simon-Taha A., Rowland M. 2003. High altitude epidemic malaria in Bamian province, Central Afghanistan. *La Revue de Santé de la Méditerranée Orientale* 9:232–239.

Reiter P. 2000. From Shakespeare to Defoe: malaria in England in the Little Ice Age. *Emerging Infectious Diseases* 6(1):1–11.

Reiter P. 2008. Global warming and malaria: knowing the horse before hitching the cart. *Malaria Journal* 7:S3.

Reiter P., Thomas C. J., Atkinson P. M., Hay S. I., Randolph S. E., Rogers D. J., Shanks G. D., Snow R. W., Spielman A. 2004. Global warming and malaria: a call for accuracy. *Lancet Infectious Diseases* 4(6):323–324.

Rodriguez D. J. 1988. Models of growth with density regulation in more than one life stage. *Theoretical Population Biology* 34:93–117.

Rogers D. J., Randolph S. E. 2000. The global spread of malaria in a future, warmer world. *Science* 289(5485):1763–1766.

Sachs J., Malaney P. 2002. The economic and social burden of malaria. *Nature* 415(6872):680–685.

Sattler M. A., Mtasiwa D., Kiama M., Premji Z., Tanner M., Killeen G. F., Lengeler C. 2005. Habitat characterization and spatial distribution of *Anopheles* sp. mosquito larvae in Dar es Salaam (Tanzania) during an extended dry period. *Malaria Journal* 4:4.

Scheffer M., Carpenter S., Foley J. A., Folke C., Walker B. 2001. Catastrophic shifts in ecosystems. *Nature* 413:591–596.

Schmalhausen I. I. 1949. *Factors of Evolution: The Theory of Stabilizing Selection.* Trans. From Russian by I. Dordick. Philadelphia (PA): Blakiston Co.

Scholte E.-J., Ng'habi K., Kihonda J., Takken W., Paaijmans K., Abdulla S., Killeen G. F., Knols B. G. 2005. An entomopathogenic fungus for control of adult African malaria mosquitoes. *Science* 308(5728):1641–1642.

Sevilla-Casas E. 1993. Human mobility and malaria risk in the Naya river basin of Colombia. *Social Science and Medicine* 37(9):1155–1167.

Shaman J., Day J. F., Stieglitz M. 2002. Drought-induced amplification of Saint Louis encephalitis virus, Florida. *Emerging Infectious Diseases* 8(6):575–580.

Shanks G. D., Biomndo K., Hay S. I., Snow R. W. 2000. Changing patterns of clinical malaria since 1965 among a tea state population located in the Kenyan highlands. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 94(3):253–255.

Shanks G. D., Hay S. I., Omumbo J. A., Snow R. W. 2005. Malaria in Kenya's western highlands. *Emerging Infectious Diseases* 11(9):1425–1432.

Shanks G. D., Hay S. I., Stern D. I., Biomndo K., Snow R. W. 2002. Meteorologic influences on *Plasmodium falciparum* malaria in the highland tea estates of Kericho, western Kenya. *Emerging Infectious Diseases* 8:1404–1408.

Shililu J., Ghebremeskel T., Mengistu S., Fekadu H., Zerom M., Mbogo C., Githure J., Gu W. D., Novak R., Beier J. C. 2003. Distribution of anopheline mosquitoes in Eritrea. *American Journal of Tropical Medicine and Hygiene* 69(3):295–302.

Shililu J. I., Maier W. A., Seitz H. M., Orago A. S. 1998. Seasonal density, sporozoite rates and entomological inoculation rates of *Anopheles gambiae* and *Anopheles funestus* in a high-altitude sugarcane growing zone in Western Kenya. *Tropical Medicine & International Health* 3(9):706–710.

Shumway R. H., Stoffer D. S. 2000. *Time Series Analysis and Its Applications.* New York: Springer.

Small J., Goetz S. J., Hay S. I. 2003. Climatic suitability for malaria transmission in Africa, 1911-1995. *Proceedings of the National Academy of Sciences USA* 100(26):15341–15345.

Smith T. A., Leuenberger R., Lengeler C. 2001. Child mortality and malaria transmission intensity in Africa. *Trends in Parasitology* 17(3):145–149.

Snow R. W., Peshu N., Forster D., Bomu G., Mitsanze E., Ngumbao E., Chisengwa R., Schellenberg J. R., Hayes R. J., Newbold C. I., Marsh K. 1998. Environmental and entomological risk factors for the development of clinical malaria among children on the Kenyan coast. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 92(4):381–385.

Somi M. F., Butler J. R. G., Vahid F., Njau J., Kachur S. P., Abdulla S. 2007. Is there evidence for dual causation between malaria and socioeconomic status? Findings from rural Tanzania. *American Journal of Tropical Medicine and Hygiene* 77(6):1020–1027.

Spielman A. 2006. Ethical dilemmas in malaria control. *Journal of Vector Ecology* 31(1):1–8.

Spielman A., Kitron U., Pollack R. J. 1993. Time limitation and the role of research in the worldwide attempt to eradicate malaria. *Journal of Medical Entomology* 30(1):6–19.

Staedke S. G., Nottingham E. W., Cox J., Kamya M. R., Rosenthal P. J., Dorsey G. 2003. Short report: proximity to mosquito breeding sites as a risk factor for clinical malaria episodes in an urban cohort of Ugandan children. *American Journal of Tropical Medicine and Hygiene* 69(3):244–246.

Stearns S. C. 2000. Life history evolution: successes, limitations, and prospects. *Naturwissenschaften* 87: 476–486.

Strahler A. N. 1973. *Introduction to Physical Geography.* New York: Wiley.

Styer L. M., Carey J. R., Wang J. L., Scott T. W. 2007. Mosquitoes do senesce: departure from the paradigm of constant mortality. *American Journal of Tropical Medicine and Hygiene* 76(1):111–117.

Tanser F. C., Sharp B., le Sueur D. 2003. Potential effect of climate change on malaria transmission in Africa. *Lancet* 362(9398):1792–1798.

Teklehaimanot H. D., Lipsitch M., Teklehaimanot A., Schwartz J. 2004. Weather-based prediction of *Plasmodium falciparum* malaria in epidemic-prone regions of Ethiopia. I. Patterns of lagged weather effects reflect biological mechanisms. *Malaria Journal* 3:41.

Thomas C. J., Davies G., Dunn C. E. 2004. Mixed picture for changes in stable malaria distribution with future climate in Africa. *Trends in Parasitology* 20(5):216–220.

Thomson M. C., Connor S. J., D'Alessandro U., Rowlingson B., Diggle P., Cresswell M., Greenwood B. 1999. Predicting malaria infection in Gambian children from satellite data and bed net surveys: the importance of spatial correlation in the interpretation of results. *American Journal of Tropical Medicine and Hygiene* 61(1):2–8.

Thomson M. C., Mason S. J., Phindela T., Connor S. J. 2005. Use of rainfall and sea surface temperature monitoring for malaria early warning in Botswana. *American Journal of Tropical Medicine and Hygiene* 73:214–221.

Trape J. F., Lefebvre-Zante E., Legros F., Ndiaye G., Bouganali H., Druilhe P., Salem G. 1992. Vector density gradients and the epidemiology of urban malaria in Dakar, Senegal. *American Journal of Tropical Medicine and Hygiene* 47(2):181–189.

Trape J. F., Pison G., Spiegel A., Enel C., Rogier C. 2002. Combating malaria in Africa. *Trends in Parasitology* 18(5):224–230.

Turchin P. 2003. *Complex Population Dynamics: A Theoretical/Empirical Synthesis.* Princeton (NJ): Princeton University Press.

van der Hoek W., Konradsen F., Perera D., Amerasinghe P. H., Amerasinghe F. P. 1997. Correlation between rainfall and malaria in the dry zone of Sri Lanka. *Annals of Tropical Medicine and Parasitology* 91(8):945–949.

Vittor A. Y., Gilman R. H., Tielsch J., Glass G., Shields T., Lozano W. S., Pinedo-Cancino V., Patz J. A. 2006. The effect of deforestation on the human-biting rate of *Anopheles darlingi*, the primary vector of falciparum malaria in the Peruvian Amazon. *American Journal of Tropical Medicine and Hygiene* 74(1):3–11.

Werner E. E., Peacor S. D. 2003. A review of trait-mediated indirect interactions in ecological communities. *Ecology* 84(5):1083–1100.

White G. B. 1972. The *Anopheles gambiae* complex and malaria transmission around Kisumu, Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 66(4):572–581.

Wilson M. L. 1994. Developing paradigms to anticipate emerging diseases: transmission cycles and a search for a pattern. *Annals of the New York Academy of Sciences* 740:418–422.

Wilson M. L. 2003. Tropical agriculture and human disease: ecological complexities pose research challenges. Pages 245–262 in *Tropical Agroecosystems,* edited by J. H. Vandermeer. Boca Ratón (FL): CRC Press.

Wilson M. L., Agudelo-Silva F., Spielman A. 1990. Increased abundance, size, and longevity of food-deprived mosquito populations exposed to a fungal larvicide. *American Journal of Tropical Medicine and Hygiene* 43(5):551–556.

World Health Organization [WHO]. 1982. *Manual on environmental management for mosquito control, with special emphasis on malaria vectors.* Geneva (Switzerland): WHO.

Yang G. J., Bradshaw C. J. A., Whelan P. I., Brook B. W. 2008. Importance of endogenous feedback controlling the long-term abundance of tropical mosquito species. *Population Ecology* 50(3):293–305.

Yasuoka J., Levins R. 2007a. Ecology of vector mosquitoes in Sri Lanka—suggestions for future mosquito control in rice ecosystems. *Southeast Asian Journal of Tropical Medicine and Public Health* 38(4): 646–657.

Yasuoka J., Levins R. 2007b. Impact of deforestation and agricultural development on anopheline ecology and malaria epidemiology. *American Journal of Tropical Medicine and Hygiene* 76(3): 450–460.

Yasuoka J., Levins R., Mangione T. W., Spielman A. 2006a. Community-based rice ecosystem management for suppressing vector anophelines in Sri Lanka. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 100:995–1006.

Yasuoka J., Mangione T. W., Spielman A., Levins R. 2006b. Impact of education on knowledge, agricultural practices, and community actions for mosquito control and mosquito-borne disease prevention in rice ecosystems in Sri Lanka. *American Journal of Tropical Medicine and Hygiene* 74:1034–1042.

Ye-Ebiyo Y., Pollack R. J., Kiszewski A. E., Spielman A. 2003. Enhancement of development of larval *Anopheles arabiensis* by proximity to flowering maize (*Zea mays*) in turbid water and when crowded. *American Journal of Tropical Medicine and Hygiene* 68(6):748–752.

Ye-Ebiyo Y., Pollack R. J., Spielman A. 2000. Enhanced development in nature of larval *Anopheles arabiensis* mosquitoes feeding on maize pollen. *American Journal of Tropical Medicine and Hygiene* 63(1):90–93.

Ye Y., Hoshen M., Louis V., Seraphin S., Traore I., Sauerborn R. 2006. Housing conditions and *Plasmodium falciparum* infection: protective effect of iron-sheet roofed houses. *Malaria Journal* 5:8.

Ye Y., Louis V. R., Simboro S., Sauerborn R. 2007. Effect of meteorological factors on clinical malaria risk among children: an assessment using village-based meteorological stations and community-based parasitological survey. *BMC Public Health* 7:101.

Yuval B. 1992. The other habit: sugar feeding by mosquitoes. *Bulletin of the Society for Vector Ecology* 17: 150–156.

Zhou G., Minakawa N., Githeko A. K., Yan G. 2004. Association between climate variability and malaria epidemics in the East African highlands. *Proceedings of the National Academy of Sciences USA* 101(8):2375–2380.

Zhou G., Minakawa N., Githeko A. K., Yan G. 2005. Climate variability and malaria epidemics in the highlands of East Africa. *Trends in Parasitology* 21(2):54–56.

Zhou G., Munga S., Minakawa N., Githeko A. K., Yan G. 2007. Spatial relationship between adult malaria vector abundance and environmental factors in western Kenya highlands. *American Journal of Tropical Medicine and Hygiene* 77(1):29–35.

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