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...
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 re-emergence, 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 high-
lands 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 spatio-temporal 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...
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 intrinsic incubation period (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

### TABLE 1

**Overview of malaria risk parameters**

<table>
<thead>
<tr>
<th>Malaria risk parameter</th>
<th>Definition</th>
<th>Mathematical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic reproduction rate</td>
<td>Number of secondary infections originating from a primary case in the absence of immunity</td>
<td>( ma^2 \frac{bp}{r (\ln p)} )</td>
</tr>
<tr>
<td>Vectorial capacity</td>
<td>Number of secondary inoculations of man per infective case per time unit</td>
<td>( ma^2 \frac{p}{r} )</td>
</tr>
<tr>
<td>Entomological inoculation rate</td>
<td>Number of infective bites per person per time unit</td>
<td>( ma \frac{s}{r} )</td>
</tr>
</tbody>
</table>

Source: Macdonald (1955)*; 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)
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; Kleinenschmidt 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 (Koenraad 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; Kleinenschmidt 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 “malaria” or “bad air”—since the earliest descriptions of the disease and its symptoms. Studies on the proximity of water bodies, either natural or man-made, 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):

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

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

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

where \( y \) is the variable of interest, \( \alpha, \delta_i, \gamma \) are regression parameters, \( \beta \) is the parameter for a deterministic time trend, and \( t \) is the time. Seasonality is included in the model via the sum \( \sum_{j=1}^{12} \mu_j d_j \), a dummy variable that takes values of 1 or 0 depending on whether \( y \) belongs to the month that is being regressed. \( e_t \) represents a random independently, identically, and normally distributed error, with variance \( \sigma^2 \) (i.e., \( e_t \sim N(0, \sigma^2) \)).

This modeling approach tests whether there are unit roots in the autoregressive process (\( \gamma = 0 \); i.e., the process being non-stationary), 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 non-parametric 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-
significant, 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 evi-

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**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:

\[ \sigma_i^2 = 1.33 \times 10^{-2}, \sigma_i^2 = 8.43 \times 10^{-2}, \sigma_i^2 = 1.39 \times 10^{-2}, \sigma_i^2 = 1.73 \times 10^{-2}. \]

(d) Linear trend from a Seasonal Auto Regressive (SAR) model. The model fitted was:

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

The parameters (±SE) are:

\[ \phi_1 = (0.44 \pm 0.05); \phi_{12} = (0.20 \pm 0.05); \phi_{13} = (0.18 \pm 0.05); \phi_{14} = (0.11 \pm 0.05); \phi_{15} = (0.24 \pm 0.05); \beta = (0.0098 \pm 0.0001); \sigma_w = 0.31. \]

The three trends were normalized to have a mean of zero.
dence 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 (Abeke 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 Peru, 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 understimates 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). Ad-
ditionally, 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:

\[
N_t = aN_{t-1}^bC_{t-1}.
\]

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 positive).

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**

<table>
<thead>
<tr>
<th>Field</th>
<th>Current observations</th>
<th>Tools/Concepts</th>
<th>Key questions/Goals</th>
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<tbody>
<tr>
<td><strong>Ecological entomology</strong></td>
<td>Rainfall and temperature</td>
<td></td>
<td>• What types of landscape are conducive for increased mosquito productivity with changes in rainfall seasonality?</td>
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<td></td>
<td>• 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).</td>
<td>• 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 &amp; Lindsay 2009; Paaijmans et al. 2009) using weather stations/sensors</td>
<td>• Mosquito habitat selection influenced by the potential for autonomization from a changing environment (Janisch 1932)?</td>
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<td></td>
<td>• Temperature increase reduces the developmental time of mosquitoes (e.g., Bayoh and Lindsay 2003)</td>
<td>• Rainfall simulators to study aquatic vector ecology (Koenraadt and Harrington 2008)</td>
<td>• How important are changes in mosquito phenology for malaria transmission? What is the role of density dependence versus climatic factors herein?</td>
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<td></td>
<td>• Differences in adult heat tolerance by mosquito species (e.g., Kirby and Lindsay 2004)</td>
<td>• Models for density dependence on adult and pre-imaginal stages (Rodriguez 1988)</td>
<td>• Are mosquito and parasite fitness affected by nectar source?</td>
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<td></td>
<td>• Density-dependence and mosquito population regulation is not fully understood (Yang et al. 2008).</td>
<td></td>
<td>• Can the vegetation composition around a household be manipulated to control malaria?</td>
</tr>
<tr>
<td><strong>Landscape and vegetation</strong></td>
<td>Mosquitoes feed on different sources of nectar, in flowers from different plant species (Yuval 1992).</td>
<td>• Gas chromatography for nectar source identification (e.g., Manda et al. 2007b)</td>
<td>• Can remote sensing and geographical information systems be used to predict the presence of (productive) larval habitats?</td>
</tr>
<tr>
<td></td>
<td>• Landscape affects presence of habitats and abundance of mosquito larvae (Fillinger et al. 2004, 2009; Minakawa et al. 2002b).</td>
<td>• Field and laboratory sugar feeding studies (e.g., Manda et al. 2007a)</td>
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<td>• Topographic modeling of landscape to understand microclimatic differences (e.g., Cohen et al. 2008)</td>
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<tr>
<td></td>
<td></td>
<td>• Remote sensing and Geographic Information Systems (e.g., Hay et al. 1998)</td>
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<th>Field</th>
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<th>Key questions/Goals</th>
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</table>
| Mosquito surveillance | ● Mosquitoes are difficult to capture in highland areas due to extremely low densities (Koenraadt et al. 2006).                                                                                                   | ● Standardized collection methods across environmental gradients with more sensitive traps, to maximize diversity and probability of capture (e.g., Njiru et al. 2006; Qu et al. 2007; Odiere et al. 2007) | ● 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? |
|                     | ● Mosquito larval habitats are dynamic (Minakawa et al. 2002b; Fillinger et al. 2004).                                                                                                                                    | ● Metapopulation and source-sink ecology (Pulliam 1988)                                                                                                                                                        |                                                                                                                                                                                                                       |
| Neglected phenomena  | Biological interventions                                                                                                                                                                                                                                                             | ● Community-based, ecologically sound, and biodiversity-friendly control strategies (Yasuoka et al. 2006a,b)                                                                                                     | ● 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? |
<p>|                     | ● 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). | ● Health impact assessments (Birley 1985): benefits of developmental strategies (e.g., dams, agriculture) can be outweighed by the exacerbation or emergence of disease transmission. |                                                                                                                                                                                                                       |
|                     | ● Misuse of insecticides and drugs can render them useless (Shanks et al. 2005).                                                                                                                                                                                                     | ● 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) |                                                                                                                                                                                                                       |
|                     | ● 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). | ● More research on the use of social marketing and traditional trading strategies for drug and bednet distribution (e.g., Mathanga and Bowie 2007)                                                                 |                                                                                                                                                                                                                       |</p>
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<tr>
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<tr>
<td>Social factors</td>
<td>● 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).</td>
<td>● 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.</td>
<td>● 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?</td>
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<tr>
<td>Evolutionary ecology</td>
<td>● Drug resistance could have evolved during the shift toward endemic malaria transmission in the African highlands (e.g., Carter and Mendis 2002).</td>
<td>● Quantitative genetics modeling approach for converging evolutionary and ecological dynamics (Hairson et al. 2005; Khinik and Kondrashov 1997)</td>
<td>● Is drug resistance a driver for malaria range expansion? How can the risk of selection for drug resistance be minimized?</td>
</tr>
<tr>
<td>Vector Fitness</td>
<td>● 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).</td>
<td>● 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)</td>
<td>● 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?</td>
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TABLE 2

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<tr>
<th>Field</th>
<th>Current observations</th>
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<tbody>
<tr>
<td>Vector Longevity</td>
<td>- Mortality is age dependent in non-malaria mosquitoes (Harrington et al. 2008; Styer et al. 2007).</td>
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<tr>
<td></td>
<td>- Vectorial capacity concept assumes that mosquito mortality is constant (Garret-Jones 1964).</td>
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<td></td>
<td>- How does senescence (i.e., the increase of mortality with age) affect vectorial capacity?</td>
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<td></td>
<td>- Chromosome banding; nuclear, ribosomal, and microsatellite molecular markers (Krzewinski and Besansky 2003).</td>
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<td>- Transplantation experiments (Diabate et al. 2008): removing larvae from original habitats to those that they do not colonize.</td>
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<td></td>
<td>- Feedback loops (Levins and Schultz 1996): mosquito density can increase if their predators are more affected by warmer temperatures than their foraging resources.</td>
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<td></td>
<td>- 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.</td>
</tr>
<tr>
<td></td>
<td>- How does competition during the aquatic life stage affect vectorial capacity?</td>
</tr>
<tr>
<td></td>
<td>- Which vectors will invade/establish in areas that undergo environmental change?</td>
</tr>
<tr>
<td></td>
<td>- How will climate change impact mosquito resources and/or their predators?</td>
</tr>
<tr>
<td></td>
<td>- Can biological control reduce vectorial capacity?</td>
</tr>
<tr>
<td></td>
<td>- What is the impact of climate change on the biological interactions involving mosquitoes?</td>
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</tbody>
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|                              | - 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).                                                                         |
|                              | - 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-subsistence 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 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 (Bogh 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 become 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 Príncipe (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 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 conditions for development 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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