Altitudinal Changes in Malaria Incidence in Highlands of Ethiopia and Colombia

A. S. Siraj et al.
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of 2, based on data from untreated macaques from both experiments) for untreated controls (Fig. 3B). Thus, a single dose of GSK744 LA delayed infection by 5 to 10 challenges (median of 8) compared with untreated macaques. Assuming a 2-week eclipse phase between the start of infection and detection of viremia, we calculated plasma GSK744 levels that coincided with the start of SHIV infection (fig. S3). All infections occurred when the plasma drug concentrations were below 0.50 μg/ml, or ~3× PAIC90. A more detailed analysis was then carried out to calculate the percent of virus challenges that resulted in infection within various ranges of plasma GSK744 concentrations (Fig. 3C). The 12 GSK744 LA-treated macaques were collectively exposed to 59 SHIV challenges at plasma concentrations ~3× PAIC90, and none resulted in infection. One of 22 challenges at plasma concentrations between 1× and 3× PAIC90 led to infection. As plasma GSK744 concentrations decreased below 1× PAIC90, 11 infections resulted from 43 virus challenges, yielding an infection rate of 25.6%. This value was lower than the 46.2% (12/26) infection rate observed in untreated macaques, but the difference was not statistically significant (P = 0.11, Fisher’s exact test). On the basis of the analysis shown in Fig. 3C, we determined that plasma GSK744 concentrations ~3× PAIC90 conferred 100% protection, whereas concentrations ≥1× PAIC90 conferred ~97% protection (see legend for calculation). No signature integrase resistance-conferring mutations were identified in breakthrough viruses (table S3). This second experiment not only defined the correlate of protection but also confirmed the results of the first experiment by showing that sufficiently high but clinically achievable GSK744 concentrations could effectively protect all macaques from repeated IR SHIV challenges.

GSK744 LA appears to be a promising next-generation PrEP agent that has afforded high-level protection against repeated IR SHIV challenges in rhesus macaques (Figs. 2B and 3B). Plasma drug levels ~3× PAIC90 provided 100% protection, whereas levels ≥1× PAIC90 provided ~97% protection (Fig. 3C). These plasma concentrations can be readily achieved in humans with quarterly 800-mg IM injections of GSK744 LA (Fig. 1B and fig. S1). Given that the half-life of GSK744 LA is 3 to 12 days in macaques whereas the half-life is 21 to 50 days in humans, we anticipate a longer-lasting protective effect in humans. Nevertheless, the proof will have to be demonstrated in future clinical trials. Optimistically, toxicity issues not withstanding, GSK744 LA has the potential to achieve in preventing HIV-1 infection what a long-acting contraceptive has achieved in preventing unintended pregnancies (29). It also stands to reason that the protective efficacy of GSK744 LA could approximate the high efficacy (>90%) observed in high-risk participants who were most adherent to daily oral FTC/TDF as PrEP (3, 6). These considerations, coupled with a favorable drug safety profile, have placed GSK744 LA on track for phase II (safety) clinical trials as well as a phase III (efficacy) trial could protect against intra- vaginal and intravenous SHIV or SIV challenges could establish the proof of concept to move into efficacy trials in other populations at high risk for HIV-1 infection.

References and Notes

8. J. Marrazzo et al., presented at the 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, 3 to 6 March 2013.
20. W. Spreen et al., paper presented at the 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, Malaysia, 30 June to 3 July 2013.

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Supplementary Materials

www.sciencemag.org/content/343/6175/1151/suppl/DC1 Materials and Methods
Figs. 51 to S3
Tables S1 to S3
References (30–33)
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Altitudinal Changes in Malaria Incidence in Highlands of Ethiopia and Colombia

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The impact of global warming on insect-borne diseases and on highland malaria in particular remains controversial. Temperature is known to influence transmission intensity through its effects on the population growth of the mosquito vector and on pathogen development within the vector. Spatiotemporal data at a regional scale in highlands of Colombia and Ethiopia supplied an opportunity to examine how the spatial distribution of the disease changes with the interannual variability of temperature. We provide evidence for an increase in the altitude of malaria distribution in warmer years, which implies that climate change will, without mitigation, result in an increase of the malaria burden in the densely populated highlands of Africa and South America.

T he impact of warming temperatures on highland malaria remains a subject of debate (1–7). Malaria is a multifactorial disease, because the etiological agent has a complex life cycle requiring an insect vector, and the factors that regulate its distribution and abundance are diverse and complex (8). Despite the expectation that global warming should lead to an increase in the altitudinal range of malaria, empirical evidence for this phenomenon is lacking, and the attribution of trends to specific factors remains difficult because of multiple drivers, including drug resistance, land-use change, human migrations, and access to health facilities (9, 10). An increasing altitudinal range implies the potential for an increased burden of malaria with climate change,
especially for countries of East Africa and South America with densely populated highlands that have historically provided havens from this devastating disease \(11\). Colder temperatures at higher altitude in these tropical latitudes slow down and even halt the development of the parasite inside the mosquito vector, decrease the rate of reproduction, and reduce the biting rate of the vector, minimizing, if not preventing, transmission \(8\).

In recent decades \(1970–2000\), pronounced increases in malaria incidence have been documented at several locations in Africa \(1, 2, 12\) for which long-term temporal records exist and which precede the greater intervention efforts of the past decade \(13\). Disease trends, no less than climate warming trends in earlier studies \(6, 14–16\), generate debate \(5\), but what has been missing is analysis of spatiotemporal records. Although range shifts have been documented with empirical evidence for the distribution of several plant and animal species \(17, 18\), similar patterns in vector-borne illnesses and pathogens of humans remain largely unexplored. An increasing incidence with altitudinal elevation in warmer years would be a clear signal of the response of highland malaria to changes in climate.

Hence, we looked for evidence of a changing spatial distribution of malaria with varying temperature for over a decade in highland regions of northwest Colombia and central Ethiopia (fig. S1). To do so, we considered temperature variability at interannual time scales rather than long-term trends. Temporal associations between malaria and climate variability have been described for endemic regions of Colombia \(19, 20\) and for epidemic regions in the highlands of Ethiopia and other East African countries \(2, 21, 22\). Thus, we specifically asked how temperature variability influences the spatial distribution of disease incidence along altitudinal gradients.

The records we used consisted of monthly \textit{Plasmodium falciparum} cases for 124 municipalities in the Antioquia region in western Colombia for 1990–2005 and for 159 administrative units, known as kebeles, in the Debre Zeit area of central Ethiopia for 1993–2005 \(23\) (figs. S1 and S2). When we clustered kebeles or municipalities on the basis of similar spatiotemporal dynamics \(23\), the resulting communities exhibited significant differences in altitude (Fig. 1). The importance of altitude to the spatial distribution of the disease was reflected in the observation of a decrease in malaria incidence as altitude increased, as expected from the concomitant decrease in temperature (fig. S6). This classic feature of the epidemiology of malaria was first reported in the 19th century \(24, 25\).

Because the absolute number of malaria cases from one year to the next can vary in relation to several demographic and environmental factors, we wanted to compare the spatial distribution of cases across years in a way that is independent of the temporal variation, including of long-term trends, in the total burden of disease. Hence, we built cumulative distribution curves for yearly cases during the epidemic season across the elevation gradient \(23\). The altitude corresponding to the median of this cumulative distribution is the “median altitude.” The median altitude changed with time to reflect the movement of the distribution up or down the altitudinal gradient. Figure 2, A and D, illustrate these patterns for two given years and shows that the median altitude for case distribution changed across years as a function of the average temperature in a critical period preceding the epidemic season (Fig. 2 and fig. S5). Thus, the median altitude for case distribution increased with mean temperature (Fig. 2, B and E), and malaria cases occurred at higher elevations in warmer years, notably in 1997 and 2002, in both regions (Fig. 2, C and F). This synchrony between continents \(26\) may be related to above-normal global temperatures that accompany El Niño events. Similar results were obtained for quantiles of the cumulative distribution above the median (fig. S7), which showed that the change in the spatial distribution did not concentrate in its center but affected its whole upper part (see also fig. S8).

Vector control by spraying residual insecticides was scaled-up after the 2002–2004 epidemic in Ethiopia and has resulted, in combination with more effective medication, in a considerable reduction of cases \(13\). Because the limited insecticide-spraying operations before 2004 may have been restricted to the lower-altitude contours that are typically considered epidemic-prone, we examined whether selective spraying of lower altitudes could account for the altitudinal shifts seen

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in the malaria case data. Specifically, because our information from Debre Zeit specifies the kebeles that have received spraying since 1994, we were able to exclude these locations from the analysis and to confirm that our results on the median altitude for the case distribution remain unchanged (fig. S9).

Spraying operations in Colombia were scaled back when eradication efforts ceased, particularly after 1993, when low-cost DDT was banned. Between 2000 and 2007, Colombia reported no insecticidal residual spraying (IRS) operations (27), and vector control is not likely to have skewed malaria’s altitudinal distribution in our Colombian study area. Rainfall and the variation of rainfall between years are also not likely to have biased our results. Over the altitude ranges in both regions, monthly rainfall during the wet season exceeds 80 mm, which is considered optimally suitable for malaria transmission (28). Furthermore, over these ranges, rainfall increases with altitude in Ethiopia but decreases in Colombia (29). Despite differences in rainfall regimes and in local vectors and vector ecology, which give rise to noticeable differences between the seasonality of malaria in both regions (fig. S3), the comparable response in both countries of malaria distribution to temperature variations highlights the importance of this climate parameter in highland areas.

To analyze the variation in incidence with temperature and altitude, we fitted a negative binomial regression to the monthly cases (23). Covariates included season, altitude, and linearly de-trended temperature (lagged by 3 months), where the latter represented a regional mean value. Model selection [based on the Akaike information criterion (AIC)] was used to compare models with different numbers of covariates and their interactions. For both regions, the best model included temperature, seasons, and altitude, as well as a mix of the two-way and three-way interactions between these covariates (Table 1). More importantly, the best statistical model showed a significant positive effect of mean temperature on the logarithm of malaria cases for both regions. This effect corresponded to a percent change in cases between 35 and 64% per 1°C for kebeles in Ethiopia at the peak of the malaria season (fig. S10 A). In Colombia, this rate ranged between approximately 10 and 80% from the highest to the lowest municipalities (fig. S10 B).

Our results showed that despite being on two different continents, in these two highland regions, increases in temperature across years extended the spatial distribution of malaria cases to higher elevations. The implication is that global warming will increase the risk of contracting highland malaria in the future. The rapid climate variations associated with the pronounced topographic heterogeneities of highland regions are poorly captured by the coarse resolution of global circulation models and their future projections (30), and the

**Fig. 2. Changes in altitudinal distribution of malaria cases with mean temperature across years.** Altitudinal cumulative distributions of cases for Ethiopia (top row) and Colombia, western region (bottom row) are shown as a function of time, as well as mean temperatures preceding the transmission season. (A and D) The altitudinal cumulative curves generated with the incidence data in two given years, together with the location of the 50th percentile and its corresponding altitude. By definition, this is the altitude at which 50% of the cases occur below and 50%, above in the altitudinal gradient. A shift of this cumulative curve to the right indicates that more malaria cases have occurred at higher altitudes in a given year. This does not mean the number of cases has increased from 1994 to 1997 but that the distribution of the disease has moved toward a higher elevation. (B and E) The corresponding scatter plots of the median altitude against these temperatures, demonstrating a movement of the distribution to higher altitudes in warmer years for the two highland regions. (C and F) show the yearly variation in the median altitude of cases (blue line), together with the mean temperatures in the critical 4-month window for the two regions (red line) (fig. S5). Uncertainty in the median value is estimated by bootstrap resampling (23) and is shown as ±1 SD in the plots. (The eastern region of Colombia exhibits similar patterns to those shown here for the western region.)
intricacies of mountain climates may complicate local climate change predictions. Moreover, highlands tend to be poorly covered by the global network of meteorological stations (29); however, because of the potential attribution of rising malaria to climate warming, station temperature records in East African highlands have received more attention (1, 14, 15). In particular, at the Debre Zeit station, significant trends in rising day and night temperatures are uncontroversial (31). In Colombia, highland areas are warming faster than the surrounding lowlands; a pattern reflected in weather station data and previously suggested by atmosphere-ocean coupled general circulation models (32, 33).

The spread of chloroquine resistance has been proposed as the main reason behind the increasing trends in malaria time series in the Kenyan highlands (9). Our retrospective data sets can be extended backward in time to the early 1980s (albeit with no spatially explicit information) for the whole aggregated region of Debre Zeit in Ethiopia and for a single municipality, Anorí, in Colombia, and for both parasites, *P. falciparum* and *P. vivax* (Fig. 3 and fig. S4) (23). Although drug resistance to chloroquine almost exclusively applies to *P. falciparum* [and this was also the case in the Debre Zeit region (34)], the longer time series of cases show similar increasing trends from the 1980s to the 1990s for both parasites in both countries. This increase occurred before the intensification of vector control and treatment of the past decade led to lower levels of malaria (13).

Climate change appears to have already influenced the burden of malaria in these regions. Specifically, the trend for malaria in Ethiopia since the 1980s (Fig. 3) is consistent with the rate of change we would expect from the interannual variation in the spatiotemporal data (23) (fig. S11). This expected change is approximately 2160 cases per degree Celsius over a season (September to December), and the value obtained from fitting linear trends to both the *P. falciparum* and temperature time series is of similar magnitude: 2310 cases. Consistent values were also obtained for Colombia (23) (fig. S11), although these values are smaller because the long time series concern a single municipality with a small population, and not the whole region studied. This means that the change expected from increasing temperatures alone can account for the retrospective temporal trend in cases observed in the recent past at both locations.

It has been argued that the global effect of climate change on malaria will be negligible as compared with the potential impact of intervention and improved socioeconomic conditions (35). However, in the East African highlands a strong temperature-determined malaria lapse rate persists (7). Elevated potential transmission intensity, driven by warmer temperatures, will require even greater control efforts, especially in countries such as Ethiopia with large populations at high elevation. In the altitude range of the Debre Zeit sector, between 1600 and 2400 m, approximately 37 million people live in rural areas at risk of malaria, which corresponds to 43% of Ethiopia’s total population. Based on Ethiopia’s current population size and the malaria lapse rate from pre-control mass survey prevalence data since the 1930s (36), we had previously estimated that a 1°C rise in temperature would result, without mitigation, in an additional 410,000 infections per year as a result of the territorial extension of malaria (11). An additional 2.8 million annual infections would occur in the population younger than 15 years of age living at altitudes where the disease would intensify and where adults already have a degree of immunity (11). These estimates were based on the assumption of a temperature-dependent shift of the disease to higher altitudes (37, 38). By supporting this assumption, our findings here underscore the size of the problem and emphasize the need for sustained intervention efforts in these regions, especially in Africa, where more highly anthropophilic vectors preclude extrapolation from the earlier and easier victories made against malaria at the fringes of temperate climates (7). Fortunately, the control of malaria at the edge of its

Table 1. Parameter estimates for the negative binomial regression model.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Ethiopia</th>
<th>Colombia (western region)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-9.3348 (0.0402)***</td>
<td>-37.1670 (5.2322)***</td>
</tr>
<tr>
<td>Season factor</td>
<td>9.6623 (0.3509)***</td>
<td>23.8540 (5.7220)***</td>
</tr>
<tr>
<td>Temperature</td>
<td>0.1880 (0.0316)***</td>
<td>1.3730 (0.2740)***</td>
</tr>
<tr>
<td>Altitude</td>
<td>-0.0037 (0.0001)***</td>
<td>-0.0004 (0.0010)</td>
</tr>
<tr>
<td>Temperature:altitude</td>
<td>-0.0002 (0.0001)***</td>
<td>-0.0002 (0.0001)***</td>
</tr>
<tr>
<td>Temperature:season</td>
<td>0.8437 (0.3919)*</td>
<td>-11.7047 (3.0020)***</td>
</tr>
<tr>
<td>Season:altitude</td>
<td>0.0091 (0.0010)***</td>
<td>0.0003 (0.0012)***</td>
</tr>
<tr>
<td>Season:temperature:altitude</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

***P value < 0.001.

Fig. 3. Temporal trends in temperature and malaria cases for the whole region of Debre Zeit (Ethiopia). The malaria cases for *P. falciparum* and *P. vivax* (top panel) are shown with the corresponding mean temperatures (bottom panel). Both *P. falciparum* and *P. vivax* cases exhibit an increasing trend from the 1980s to the end of the 1990s. So does mean temperature by 1°C in 378 months (estimated as a linear trend). An increase of 1°C corresponds to an additional 2166 cases during the main transmission season (from September to December). This malaria increase over time is consistent with what is expected from the trend in temperature, given the described change in cases with the interannual variation of temperature over a shorter time period (23) (fig. S11). A long-term trend in cases is also shown for Colombia but for a single municipality (fig. S4).
altitudinal distribution is considerably easier than in highly endemic, lower-elevation regions. Despite Africa’s exceptionally efficient vectors, an early eradication pilot scheme in highland regions shows that malaria transmission at altitudes in excess of 1130 m (3700 feet) can be fully interrupted (39). Public health policies should therefore be formulated that mitigate the effects of climate change on malaria in highland regions, including those policies that extend and sustain the network of diagnostic and monitoring facilities. These measures should further contribute to the early warning of epidemics and assist global malaria elimination.

References and Notes
23. Materials and methods are available as supplementary materials on Science Online.

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