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Journal
Trends in Parasitology, 21(2)

ISSN
1471-4922

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Publication Date
2005-02-01

DOI
10.1016/j.pt.2004.11.002

Peer reviewed

Research Focus Response

Climate variability and malaria epidemics in the highlands of East Africa

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The causes of the recent re-emergence of malaria in the East African highlands probably involve a complex interplay among multiple factors, including climate, land use, topography, inadequate use of antimalarial drugs and drug resistance, socioeconomic status, health policy and public health control measures. It is important to determine the relative contribution of these factors. In our study, we statistically attributed the effects of autocorrelation, seasonality and climate variability to the temporal variation in the number of malaria patients in several highland sites in East Africa. We found that in three out of seven sites, climate variability contributed more variance to malaria patient numbers than did autocorrelation and seasonality. In all seven study sites, we found highly significant nonlinear, synergistic effects of the interaction between rainfall and temperature on malaria patient time series.

Introduction

In response to our study [1], Hay *et al.* [2] raised the question that correction for multiple t testing would reduce the number of significant results on climate variability. In our report [1], we found that eight of 21 t tests (38%) showed significant increases in climate variability (annual variance in maximum and minimum temperature, and rainfall) between the periods 1978–1988 and 1989–1998 ($P<0.05$). When the type I error level of each test is set at 0.05, we would expect only one ($0.05\times 21=1.05$) of the 21 tests to be significant because of chance. However, the number of tests with significant results was greater than one, suggesting that increased climate variability has occurred in the study sites. Although we did not test the variance in the number of malaria patients, we showed that the proportion of epidemic months in the period of 1989–1998 was nearly twice that of the period 1978–1988 (see Table 2 in Ref. [1]). Such a substantial increase in the proportion of epidemic months coincided with a parallel increase in climate variability, and statistical tests support a strong association between them [1]. We did not adjust annual human population growth rates because there was strong evidence for an increased number of hospitals, health centers and clinics as human population size increased in these countries during the study period.

Table 1 presents the change in human population size and the number of health facilities in Rift Valley and Nyanza provinces, in Kenya from 1981 to 1993 and in Uganda from 1987 to 2001 (health facility data in Ethiopia are not available). We have chosen these two provinces of Kenya because the three study sites (Kericho, Nandi and Eldoret) are in Rift Valley province, and one site (Kisii) in Nyanza province. The rates of increase in human population size and the total number of health facilities are remarkably similar (Table 1). For example, over the 12-year period, the human population size increased by 54.6% and 39.9% in Rift Valley and Nyanza provinces, respectively, and the total number of health facilities increased by 50.8% and 64.9%, respectively. Although the number of health facilities at specific sites cannot be inferred from the provincial-level data, there is no reason to assume that the number of health facilities in the highlands – where the economic situation is generally better, compared with the lowlands – has not increased at a rate comparable to the provincial average. Thus, it is fairly reasonable to assume that the size of the human population served by each hospital or health facility remained similar during the study period. By contrast, it is not reasonable to assume that the number of hospitals or health facilities did not change during the 20-year study period, and it is not appropriate to assume that the size of the human population served by each hospital or health facility changed according to the rate of increase in the size of the human population. In the case of Kericho, the population eligible for healthcare remained largely unchanged ($\sim$50 000 people) during the study period [3].

The statistical model and stepwise multiple regression analysis used in our report [1] have an advantage over other methods, in that we were able to partition the temporal variance in malaria patient numbers into two variance components: the variance due to autoregression and seasonality, and the variance due to climate variability. The stepwise regression method selected only those variables that showed significant correlations with the malaria data. Although the models contained nine parameters (the constant term was not counted as a parameter), only 3–6 parameters (average = 4.7 for the seven sites; see Table 3 in [1]) were selected and these produced excellent fitting of the malaria patient dynamics

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Available online 25 November 2004

Table 1. Changes in human population size and health facilities in the Rift Valley and Nyanza provinces, Kenya, from 1981 to 1993, and in Uganda from 1987 to 2001

Country	Province	Variable	Year 1981	1985	1990	1993	Increases from 1981 to 1993
Kenya	Rift Valley	Human population size (in thousands)[a]	3735	4358	5217	5775	54.6
		Total number of health facilities[b]	502	447	583	757	50.8
		Hospitals	52	51	61	64	23.1
		Health centers	86	61	65	155	80.2
		Health subcenters and dispensaries	363	335	457	757	108.5
	Nyanza	Human population size (in thousands)[a]	2621	2908	3353	3666	39.9
		Total number of health facilities[b]	219	224	345	359	64.9
		Hospitals	38	38	42	47	23.7
		Health centers	39	47	49	76	94.9
		Health subcenters and dispensaries	142	139	254	236	66.2
			Year 1987	1992	2001		Changes from 1987 to 2001
Uganda		Human population size (in thousands)[a]	15 666	17 475	23 986		53.1
		Total number of health facilities[c]	580	1047	3073		429.8
		Hospitals	79	86	104		31.6
		Health centers	89	184	159		67.4
		Health subcenters and dispensaries	412	777	2810		582.0

[a]Human population data for Kenya were estimated from Kenya national population census conducted in 1969, 1979, 1989 and 1999 (http://www.library.uu.nl/wesp/populstat/populhome.html), assuming a constant annual increase rate between two consecutive censuses but varying rates among decadal censuses. Uganda population data were obtained from the same web source.
[b]Health facilities data for Kenya are from Table 8 of Ref. [18] (available at http://www.hsph.harvard.edu/ihsg/publications/pdf/No-20.PDF). See Ref. [11] for definition of hospital, health center and health subcenter and dispensary.
[c]Health facilities data for Uganda are from http://www.health.go.ug/.

data. Thus, the criticism that the model has too many parameters, leading to good data fitting, is inappropriate. We did not explicitly include the variance measures for temperature and rainfall in the model because adding the variance terms [mean monthly minimum or maximum temperature or monthly rainfall minus the average values of these variables (i.e. constants) over the study period] would only change the regression coefficients, without affecting the results concerning the variances attributed to autoregression and seasonality, and climate variability; nor would the overall model fitting be affected. Addition of the variance measures into the model would make it more complex, although the variability term would be represented more explicitly. Similarly, inclusion of each of the lagged climate variables in the model, rather than using the average of climate variables for the months that showed significant cross-correlations, would only add more parameters and complexity to the model, without substantially changing the results concerning the proportion of variance explained by climate variability. Our model, using only three factors (autoregression, seasonality and climate variability) and 3–6 parameters, explains 65–81% of the temporal variance in malaria patient numbers. The general model (Equation 1 in [1]) can be used in any sites, although the model parameter estimation should be conducted for individual sites because of high spatial variations in climate condition, vectorial system, land use, topography, socioeconomic status, vector and disease control, and other factors influencing the response of mosquito vectors and parasites to climate variability. For example, whereas *Anopheles gambiae* populations are very sensitive to rainfall, the same is not true for *Anopheles funestus* [4]. Similarly, each site might have specific rainfall thresholds, depending on the rates of evapotranspiration and drainage efficiency. It should be noted that vectorial systems, malaria transmission intensity [5,6] and, thus, clinical immunity [7] – factors crucial in the outcome of malaria infection – vary a great deal among sites, even within one region with similar temperatures and rainfall. Our results (see Table 3 in [1]) strongly suggest that the malaria early warning systems [8] should take account of the high spatial variations in climate and other factors.

We recognize that the causes of malaria epidemics involve climate, biological and socioeconomic factors and their interactions. Because the time-series data for some of these factors were not available, in our statistical models we had to attribute these unknowns to the error term. Our models left 19–35% of variance in malaria patient numbers unexplained. Because of such large residuals, model misspecification test results (i.e. homoscedasticity, autocorrelation and normality of the estimated residuals) cannot be interpreted appropriately. The question that we wanted to address was whether climate factors were significantly associated with malaria data and, if so, how much variance the climate factors explained, we found that the stepwise regression analysis had adequately addressed the question. Hay *et al.* [2] correctly pointed out the mislabeling of the Kericho inpatient data in our report, and we regret the error.

We disagree with the comments by Hay *et al.* [2] concerning misrepresentation of geographical expansion of the malaria epidemic in Kenya and drug resistance issues. Firstly, the Kenyan Government declared 15 districts in the highlands of western Kenya to be prone to malaria epidemics in late 1990s, an increase from three districts during the late 1980s [9]. The paper by Githeko

and Ndegwa [10] was one of the first reports in the scientific literature to state this fact.

Secondly, drug resistance alone cannot lead to malaria epidemics in the highlands for several reasons. For example, if drug resistance were the main driving force, the effects of drug resistance on malaria patient numbers should increase proportionally to resistance until a new drug is introduced. Thus, we would expect the number of malaria patients to increase gradually over time (until the introduction of a new drug) but it would not exhibit negative monthly case anomalies. By contrast, we observed dramatic fluctuations in the malaria patient numbers during the study period. Although the Kenyan Government introduced sulfadoxine-pyrimethamine as the first-line antimalarial drug in 1998, when treatment efficacy was high (average adequate clinical response $>90\%$; [11]), a major epidemic occurred in the Kenyan highlands in 1998 following the 1997–1998 El Niño event [1,12–14]. Moreover, drug resistance could not explain the sporadic malaria epidemics in the Kenyan highlands in the 1920s to 1950s [15], when the problem of drug resistance was insignificant. In addition, statistical association between malaria epidemics and increased drug resistance is lacking.

Thirdly, the malaria transmission climate suitability index in the report of Small *et al.* [16] did not consider the synergistic effects of temperature and rainfall on malaria transmission – which are more important than their individual effects, as demonstrated in our report [1]. In addition, the trend analysis of malaria transmission suitability changes over a period of 84 years [16] was based on crude resolution and spatially extrapolated climate data, and also assumed a static vectorial system throughout Africa. Furthermore, the 80 mm rainfall threshold for malaria vectors is only applicable to a particular vectorial system, and not to the whole African continent. We thus question the appropriateness of inferring the role of climate in malaria transmission in the highlands using continent-scale suitability maps because of the high spatial variation in climate conditions, topography and agricultural practices [17].

In sum, our report [1] suggests that assessing the impact of climate change on malaria transmission requires consideration not only of annual mean temperature changes but also, more importantly, on the extent of temperature and rainfall intermonth and interannual variability. The accuracy of our statistical model, particularly with respect to the timing of malaria epidemics, can be validated using the upcoming climate and epidemiological data. We would also like to emphasize that thorough analyses of the time-series data concerning other potentially important factors such as land use, socioeconomic status, drug resistance and public health control measures are needed to better understand the mechanisms for malaria epidemics in the East African highlands.

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1471-4922/$ - see front matter
doi:10.1016/j.pt.2004.11.002