Malaria early warning in Kenya

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Kenya displays large spatiotemporal diversity in its climate and ecology. It follows that malaria transmission will reflect this environmental heterogeneity in both space and time. In this article, we discuss how such heterogeneity, and its epidemiological consequences, should be considered in the development of early warning systems for malaria epidemics.

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A long-held approach to dealing with spatial complexity in malaria epidemiology has been to classify malarious zones along a stable–unstable gradient[1,2]. Stable malaria exists where the basic reproductive rate or number of malaria (R_0) regularly exceeds unity. R_0 is described by Eqn 1:

$$R_0 = \frac{a^2 bcmp^n}{r - (\log_e p)} \quad [1]$$

where a is the daily rate at which mosquitoes bite humans, b is the transmission coefficient of *Plasmodium* spp between an infected person and an uninfected mosquito, c is the transmission coefficient of *Plasmodium* spp between an infected mosquito and an uninfected person, m is the mosquito density in relation to man, p is the daily probability of mosquito survival, n is the time taken for completion of extrinsic parasite development and r is the rate of recovery of humans from infection[3]. It becomes clear from such an expression that maximal stability is favoured when extrinsic development of the parasite is short, when anophelines and humans are highly susceptible to infection, and when the vectors have a low mortality rate and bite humans frequently. Where such conditions are met and *Plasmodium falciparum* malaria transmission is stable, the prevalence of infection is high and endemicity is relatively insensitive to climatic changes. The constant high challenge to the local population stimulates strong immunity and a consequent decrease of clinical disease episodes among adults. In stable areas, smaller vector populations can maintain transmission so that the presence of mosquitoes without malaria is rare.

Africa can be viewed as stable for *P. falciparum* malaria transmission, with instability increasing towards its latitudinal and altitudinal limits. Instability occurs when R_o drops seasonally below one. This occurs towards the northern fringe in Africa, where arid conditions lead to decreased opportunities for mosquito breeding and increased larval and adult mortality, as well as when moving up into highland areas, where the extrinsic incubation period of the parasite is significantly prolonged owing to a decrease in average temperature. At the southern fringe of Africa, a combination of these factors operates. In areas where malaria is unstable, its epidemiology is quite different. The probability that an individual mosquito will pass on an infection is small and, as a consequence, malaria usually occurs only when vector populations are large. The presence of mosquitoes without malaria is more common and small changes in environmental conditions can have relatively dramatic effects on the probability of parasite transmission. Often prolonged periods of disease absence are punctuated by epidemics (Box 1), the severity of which is conditioned by the size of the nonimmune population that has developed in the interval through births, immigration and loss of functional immunity. Low population immunity also results in all age groups succumbing equally to the disease.

To demonstrate these points and their implications for malaria early warning in Kenya, two epidemiologically distinct areas are contrasted: Wajir, in the arid north-east, and Kericho, in the cooler and wetter western highlands.

Wajir

Wajir exemplifies the epidemiology of an unstable malaria zone limited by rainfall. Figure1a shows a spider-plot of the average number of hospitalized cases of *P. falciparum* malaria each month. The frequency of severe malaria is more common in adults, as a consequence of low levels of population immunity. The reported numbers are thought to be distributed in favour of adults, owing to behavioural differences in exposure and the increased likelihood of adults being able to command resources for medical attention. When epidemics occur in such areas, the resulting impact on public health can be devastating[4]. In Wajir town, it has been estimated that there were 4112 deaths, approximately 5% of the population, during the 1997–1998 epidemic (Fig. 2a) and 10 545 deaths in the Wajir province as a whole[5]. Figure 2 demonstrates the clear relationship between malaria cases and rainfall at Wajir; following significant rainfall it takes three months for the peak in malaria cases to be manifest. Simple techniques could therefore be used to predict future case numbers based on rainfall measurements alone, making epidemic warning straightforward in rainfall-limited unstable malaria zones. Moreover, as epidemics are intermittent in such areas, local healthcare facilities are often unprepared for such events and the case for epidemic preparedness through early warning systems is strong[5].

The role of remote sensing

Meteorological satellite sensors provide a mechanism for the routine measurement of climate over extensive areas where the distribution of meteorological stations

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Box 1. Defining epidemics

MacDonald describes a malaria epidemic as follows[a]:

'An epidemic is an acute exacerbation of disease out of proportion to the normal to which the community is subject ... Epidemics are common only in zones of unstable malaria, where very slight modification in any of the transmission factors may completely upset equilibrium, and where the restraining influence of immunity may be negligible or absent, and they therefore show a very marked geographical distribution.'

We find such a limited classification desirable because it helps define epidemiologically distinct scenarios for malaria epidemic warning.

a MacDonald, G. (1957) Epidemics. In *The Epidemiology and Control of Malaria*, pp. 45–62, Oxford University Press

is often poor[6,7]. Moreover, remotely sensed coverages can provide information in a more accurate and timely fashion than do alternative techniques, such as spatial interpolation of widespread rainfall data[8]. A provisional system to monitor rainfall anomalies in the arid areas of sub-Saharan Africa (SSA), based on information collected routinely for famine early warning in Africa[9,10], is currently feasible and could be adopted for early warning of malaria outbreaks in such unstable areas. The satellite data on which this would depend are in the public domain and currently issued in near real-time on the Internet[11].

It is less obvious that thermal information retrieved by meteorological satellites[12,13] will enable temperature anomalies to be monitored where unstable malaria conditions result from low temperatures (generally those regions at high altitude and southern latitudes in SSA). Although promising, many problems remain in retrieving temporally and spatially consistent temperature readings from meteorological satellite series[14]. A more comprehensive consideration of the future role of remotely sensed technologies in malaria early warning, control and public health can be found in Refs 15 and 16 and a historical perspective and success found in Refs 17–19.

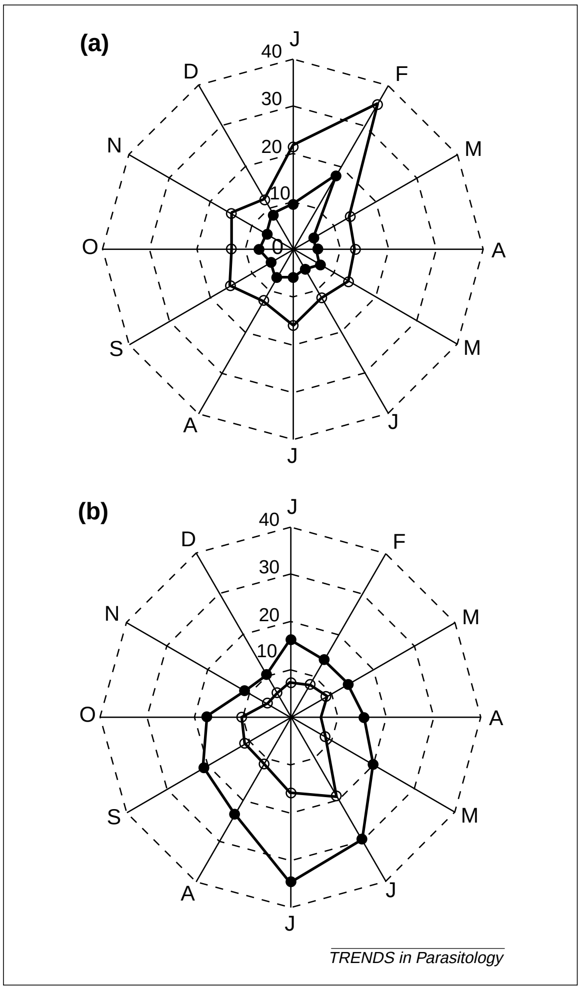

Fig. 1. Spider-plots of malaria admissions in Wajir (a) and Kericho (b). The data are monthly averages for the 1991–1998 and 1965–1998 periods, respectively. Adult cases (unfilled circles) and child cases (filled circles) are shown.

Kericho

The epidemiology of malaria is very different to Wajir in the tea estates of Kericho in the western highlands of Kenya[20,21]. Although Kericho is above 2000 m, and hence considered by some to be an unstable malaria area[22,23], conditions are usually suitable for transmission (Fig. 3a) throughout the year and this annual challenge leads to significant clinical immunity among adult populations, so that the disease tends to be focused in largely nonimmune cohorts of children (Fig. 1b). This reflects a more stable malaria epidemiology and leads to the question; can climate alone be used to predict malaria cases in Kericho accurately?

SDA analysis of Kericho epidemiological and meteorological time-series

The time-series technique of spectral density analysis (SDA)[24,25] has been used to investigate the periodicity in a unique 30-year series of malaria admissions data and contemporaneous temperature and rainfall data from Kericho[26]. This work is reviewed here, first, because the technique has the potential to separate seasonal versus longer-term cycles in the retrospective analysis of epidemiological data and, second, because the implication of the results with respect to epidemic early warning merits commentary. SDA was first used to investigate the periodicity of malaria epidemics in the Punjab[27] following its very early application to measles epidemiology[28].

The monthly epidemiological and meteorological time-series were first made stationary ('de-trended') using a moving average of 61 points (months), which is longer than any cycles of interest in these data. Stationarity is a prerequisite for many time-series analysis techniques[24]. Practically, this results in a transformation of the time-series that allows a degree of replication such that formal inferences are possible. The SDA was then performed on the raw data from which the moving average was subtracted (Fig. 3a). SDA separates the total variance of a time-series into

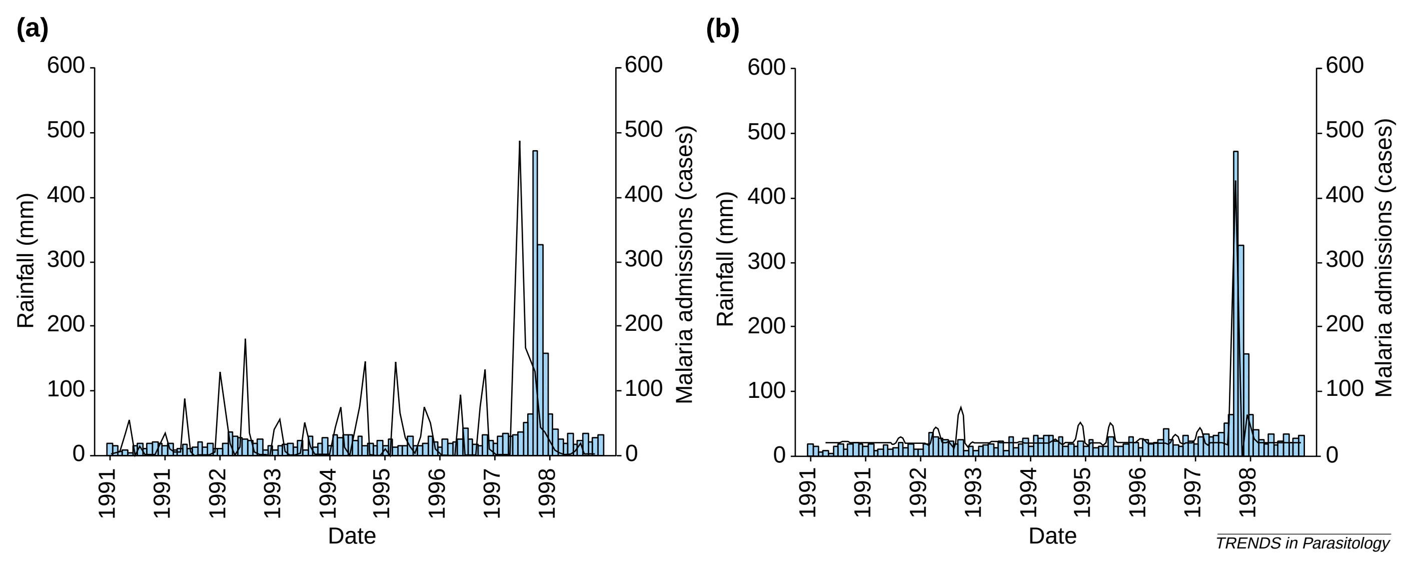

Fig. 2. Malaria cases and rainfall by month (1991–1998) for Wajir, Northern Kenya, are shown in (a). The bars are malaria cases and the black line rainfall totals. Observed (blue bars) and predicted (black line) malaria cases in Wajir are shown in (b). The prediction is based on a simple quadratic relationship between present cases (x) and rainfall (y) 3 months previously; where $x = 19.9635 - 0.0399y + 0.0018y^2$. The 20-case baseline is thought to represent the background of malaria from very localized transmission, i.e. from around water sources, and imported malaria cases.

orthogonal and thus uncorrelated sinusoidal components at different frequencies so that, in a standard spectral density plot, the area under the curve represents the total contribution of those frequencies to the total variance[25]. The SDA for the malaria incidence data is shown in Fig. 3b and plotted against the period to make interpretation easier. The variance in the series is partitioned into two domains; events with an annual cycle and events with a super-annual cycle with a mean period of approximately three years. Therefore, malaria cases vary seasonally but, every 36 months, a peak in malaria incidence is observed. Most of the variance of contemporaneous temperature and rainfall data (not shown) is associated with cycles of ≤1 year almost none occurs in cycles of lower frequency (i.e. longer period). The relationship between climate and malaria seasonality is hence complicated by a strong between-year signal that is not related to climate.

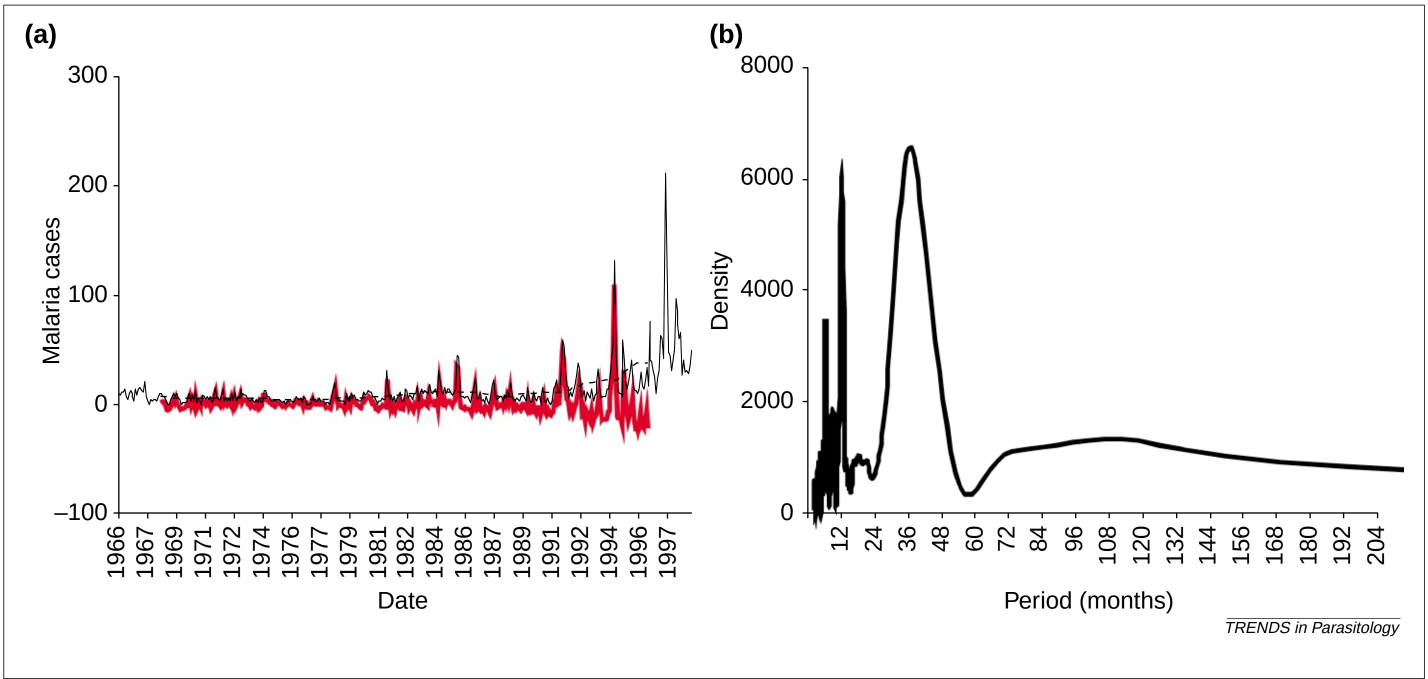

Fig. 3. (a) The monthly incidence (cases per 100 000) of *Plasmodium falciparum* malaria incidence in Kericho from April 1965 to December 1998 are shown in black. The dashed line shows a moving average of 61 months and the bold red line the stationary malaria incidence series (original value – moving average) on which spectral density analysis was performed. Note that cases are treated in most months and that the dramatic post-1980 increases in case numbers has been argued to result from the development of drug resistance[21]. (b) The spectral density plot for malaria incidence at Kericho. A Tukey–Hamming window of three points was applied to smooth the spectral density plot. Details of the variance structure from the periodogram (unsmoothed spectral density plots of frequency) show that annual frequencies and less account for 69.8% of the total variance in the time-series and super-annual frequencies for 30.2%.

These between-year cycles are to be expected from basic population dynamics. In unforced susceptible, exposed, infectious, recovered (SEIR) models of directly transmitted diseases, incidence is predicted to exhibit damped oscillations with an approximate inter-epidemic period (T) (Eqn 2):

$$T \cong 2\pi[(D + D')A]^{1/2} \quad [2]$$

where D is the latent and D' the infectious interval of the disease and A, the average age of first infection[29]. In models that incorporate demographic or environmental stochasticity, resonance ensures these oscillations are sustained, provided the population is large enough for the pathogen to avoid extinction. Such interactions occur regardless of changes in the abiotic environment, although it has been suggested that many forcing mechanisms, including seasonality, should help to maintain these oscillations[30].

Cyclical behaviour is observed in directly transmitted diseases such as measles, mumps and pertussis[31,32] and for vector-borne diseases such as malaria[27], human trypanosomiasis[33] and kala-azar[34]. Equation 2 provides one of a possible number of interpretations of cyclical behaviour (although mechanisms such as negative strain interactions[35] might also be important). Regardless of whether epidemiological modelling or time-series decomposition techniques provide an estimate of the inter-epidemic period, forecasting techniques that can describe such dynamics will be required for 'epidemic' prediction in endemic areas.

Implications for early warning systems

We argue that the implementation of malaria early warning systems should be guided as much by Macdonald's insights[1,3], as by the desire to apply new epidemiological tools. The evidence from two areas widely regarded as epidemic – Wajir and Kericho – highlight the contrasting epidemiological features of transmission and their public health impact. Systems for epidemic warning that ignore parasite and host population dynamics in endemic areas are unlikely to be sufficiently robust to capture super-annual variation in disease risk. In stable malaria areas where population dynamic effects are strong, climate alone will not be sufficient for early warning systems. Greater degrees of sophistication will be required to develop predictive skill for such areas.

In the light of these analyses, remotely sensed malaria early warning systems are being developed to provide real-time rainfall and temperature anomaly information for arid and high-altitude epidemic-prone districts in Kenya. Attempting to extend such systems to the stable malarious districts of the country is a longer-term objective. The application of new technologies such as remote sensing to malaria early warning must not be blind to basic epidemiological processes, even if they are not entirely understood. As George MacDonald[1] warned:

> 'The causes of these waves cannot be certainly determined and must largely remain the subject of inspired guesswork. It is certain that they were on the whole small, representing minor increases and decreases in the facility of transmission, which explains the difficulty in discerning them accurately.'

We hope, however, that the spectral density techniques discussed will contribute to an increased understanding of such 'waves' and ultimately reveal ways in which they might be predicted.

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Trypanosoma vivax – out of Africa

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***Trypanosoma vivax* is a blood parasite of ruminants that was introduced into Latin America in cattle imported from Africa, possibly in the late 19th century. The parasite has now spread to ten of the 13 countries of the South American continent, often resulting in a severe wasting disease and death. Here, we review the current state of knowledge about this parasite and the problems faced by animal health agencies in controlling the disease.**

Of the three main species of tsetse-transmitted trypanosomes affecting ruminants in sub-Saharan Africa, only *Trypanosoma vivax* has spread beyond the bounds imposed by its vector in Africa and established itself in South America. It is impossible to place an exact date on its introduction as there are records of cattle being imported into South America from Africa in support of European colonization since 1545 (Ref. 1). Although morphometric studies[2], DNA fingerprinting[3] and isoenzyme profiling[4] suggest a West African origin for New World *T. vivax*, it differs from African *T. vivax* in the diversity of its surface antigens, and its inability to infect tsetse and grow *in vitro*[5].

History of *T. vivax* in South America

First described in oxen suffering from an emaciating disease in French Guiana[6], *T. vivax* was subsequently identified in the blood of cattle in French Guiana (1919), Venezuela (1920), Guadeloupe (1926), Martinique (1929), Colombia (1931), Surinam (1938), Panama (1941), Guyana (1952) and Brazil (1972); and detected through antibodies to *T. vivax* in cattle from El Salvador (1977), Costa Rica (1977), Ecuador (1977), Peru (1977), Paraguay (1977) (reviewed in Ref. 7) and, most recently, the lowlands of Brazil[8] and Bolivia[9] (Fig. 1), It is impossible to tell, however, whether these reports represent spread from the initial introduction or the detection of existing infections that had been previously unreported, overlooked and/or confused with other diseases. Nevertheless, the recent reports from the Pantanal area of Brazil are likely to be linked to the accelerated construction of roads in the interior of Brazil in the early 1990s; these probably provided a conduit for the introduction of infected animals from the north into this important cattle-rearing area. There were outbreaks of severe disease in the Pantanal area ascribed to *T. vivax*, characterized by emaciation, abortion and death. Increased cattle trading between the Pantanal area of Brazil and neighbouring Bolivia, again attributed to better road communications and also to decreased cattle prices in Brazil, resulted in the introduction of the parasite into Bolivia, with subsequent severe disease and up to 40% mortality[10]. Current estimates indicate that more than 11 million head of cattle with a value of more than US$ 3 billion are at risk from *T. vivax* infection in the Brazilian Pantanal and Bolivian lowlands, with potential losses in excess of US$ 160 million[10].

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Transmission of *T. vivax*

The unregulated movement of infected animals across national and international borders is probably the principal way that the parasite spreads to new areas. Once introduced into an area, however, the method of subsequent transmission is not clear. Non-cyclical or mechanical transmission by blood-sucking flies, such as tabanid or stable flies (*Stomoxys* spp), is usually cited as the principal method of transmission. It has been shown that New World *T. vivax* can be transmitted by several biting fly species[11,12], and in many endemic areas there is strong circumstantial evidence that biting flies could be involved in the transmission of *T. vivax* in South America[13,14]. However, in mainland Africa there is no evidence of *T. vivax* infection outside the distribution range of tsetse, despite the presence of high numbers of biting flies in areas such as the Sahel region. Furthermore, *T. vivax* has disappeared in areas such as Zanzibar,

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