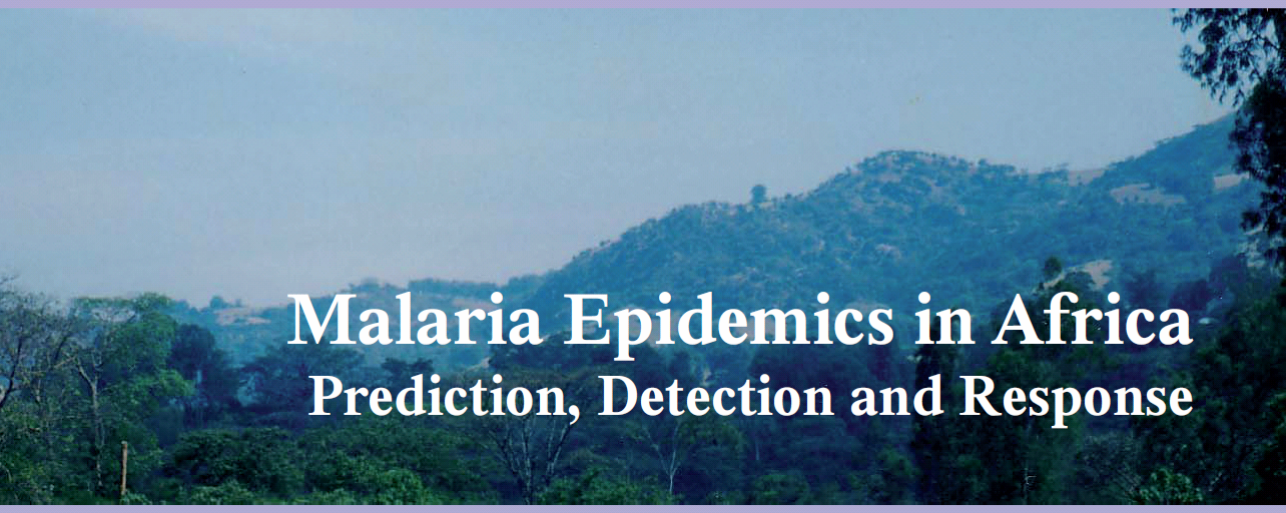
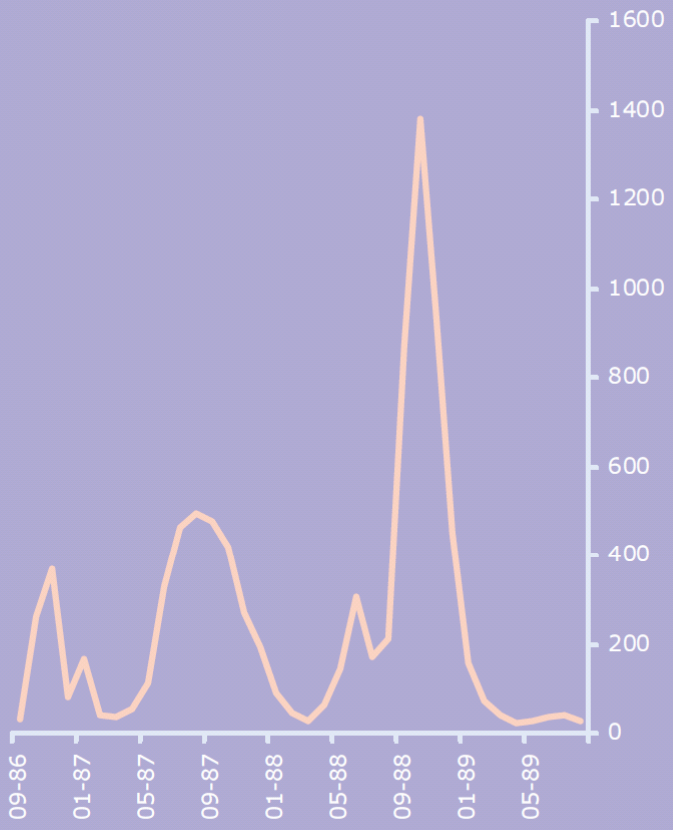


Malaria Epidemics in Africa
Prediction, Detection and Response



Tarekegn Abose Abeku

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Malaria Epidemics in Africa
Prediction, Detection and Response

Malaria-epidemieën in Afrika
Predictie, Detectie en Respons

Thesis

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Tarekegn Abose Abeku

born at Ghimbi (Wollega), Ethiopia

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Cover photo and illustration: A malaria epidemic prone area in western Wollega (at Dalo Gambela), Ethiopia. The graph shows a major epidemic that affected the same area.

To Lisa

Contents

Publications reprinted in this thesis

Chapter 2: Abeku TA, Hay SI, Ochola S, Langi P, Beard B, de Vlas SJ, Cox J (2004) Malaria epidemic early warning and detection in African highlands. *Trends in Parasitology*, **20**: 400-405.

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Chapter 6: Abeku TA. Response to malaria epidemics: available options and associated challenges. (*Submitted*).

1

General introduction

1.1 The global malaria problem

Malaria kills at least one million people worldwide every year and 80% of the deaths occur in Africa south of the Sahara (RBM *et al.* 2005). According to a new estimate using a combination of epidemiological, geographical and demographic data, there were 515 million clinical episodes of *Plasmodium falciparum* malaria (range 300 million—660 million) in the year 2002, 50% more than those reported by the World Health Organization (WHO) (Snow *et al.* 2005). Malaria has become a major obstacle to economic growth in endemic developing countries (Gallup and Sachs 2001).

In most endemic countries, there are inadequate human, logistics and financial resources and poor infrastructure to deal with the malaria problem. The Abuja Declaration issued by African Leaders in 2000 set a goal for the Roll Back Malaria (RBM) initiative to reduce malaria-related mortality in Africa by half by the year 2010, calling on governments, international organizations and communities to intensify the fight against this deadly disease (RBM 2000). To achieve this goal, it was recommended to significantly increase access to prompt and effective treatment and insecticide-treated nets (ITNs) by those most at risk, and to intermittent preventive treatment (IPT) for pregnant women. Whether this ambitious goal will be realized is yet to be seen but there is a renewed international effort mainly through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) to alleviate the problem of malaria in many countries (WHO/UNICEF 2003).

Resistance to antimalarial drugs such as chloroquine and sulfadoxine-pyrimethamine (SP) is a major problem in providing effective treatment in Africa. As a result, several African countries had changed their national drug policy and adopted the more effective artemisinin-based combination therapy (ACT) (RBM *et al.* 2005). However, the universal implementation of this policy is still at its early stages largely due to the imperative cost of these drugs which is about 10 times that of the traditional drugs. ITN distribution has increased, but the coverage is still very low in many countries. Many countries have also started implementing IPT for pregnant women (RBM *et al.* 2005).

1.2 Malaria transmission

Before we discuss factors that determine the spatial and temporal distribution of malaria, it is necessary to consider the stages of the life cycle of the parasite that are relevant in the study of transmission of the disease. Among the four

species of the protozoan parasites of the genus *Plasmodium* that cause human malaria, *P. falciparum* is the most pathogenic and widely distributed in Africa. The other species (*P. vivax*, *P. ovale* and *P. malariae*) have limited distribution in Africa and are relatively less life-threatening.

The life cycle of *P. falciparum* can be divided into three different phases, namely the sporogonic, exo-erythrocytic and erythrocytic cycles (Fig 1.1). The sporogonic cycle takes place within the mosquito vector and is affected by environmental factors. It is an important stage of the parasite's cycle in terms of determining the probability of transmission. After the mosquito ingests blood with the male and female gametocytes, gametes will be formed within the mosquito's midgut. The gametes unite to form the zygote. After transforming into an ookinete, it penetrates the wall of the midgut and becomes a round oocyst. The nucleus divides inside the oocyst repeatedly and a large number of sporozoites are produced. When the sporozoites are fully developed, the oocyst bursts. The sporozoites are released into the mosquito's body cavity and migrate to the salivary glands. The time necessary for the development of the sporozoites varies with temperature and to a smaller extent with the species of the malaria parasite and with humidity, but in tropical temperatures it is generally about 8-15 days long. Sporozoites are the infective stage of the parasite and are injected with saliva when the mosquito next feeds. The parasites migrate to the liver cells where they multiply for 7-12 days during the exo-erythrocytic cycle. The infected liver cell will burst, releasing merozoites into the bloodstream, where they invade the red blood cells and multiply again. The infected red cells are destroyed, the parasites invade fresh red blood cells and the erythrocytic cycle is repeated. During the erythrocytic cycle, gametocytes are also formed.

A female *Anopheles* mosquito ingests blood which is necessary for maturation of eggs. The most important vector species in African highlands include *A. gambiae* s.s., *A. arabiensis* and *A. funestus*. The former two species mainly breed in open, sun-lit, small and temporary rain pools and sometimes pools formed in streams and rivers resulting from draught conditions. *A. funestus* breeds in permanent water bodies such as swamps, ponds and edges of lakes.

The vector's life cycle is mostly affected by the environment and is also obviously relevant in the study of malaria transmission. Mosquitoes have four different stages in their life cycle: the egg, larva, pupa and adult. The time taken for the aquatic stages to develop depends on temperature and nutritional factors in their environment. Development is shorter at higher temperatures.

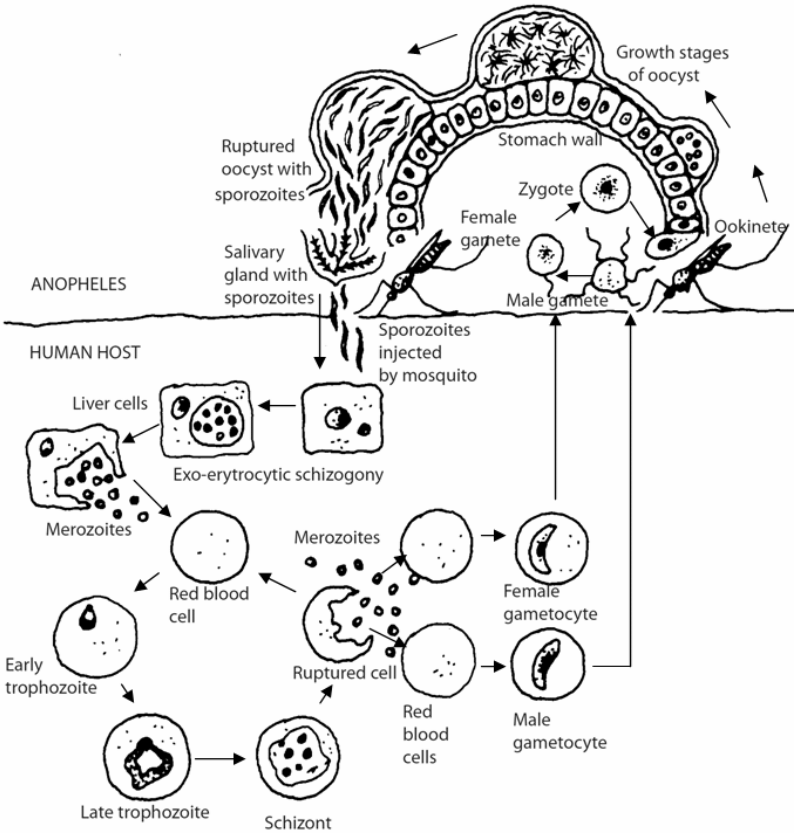

Figure 1.1 Life cycle of *Plasmodium falciparum.*

Blood meals are generally taken every 2-3 days, followed by the laying of the next batch of eggs. The feeding frequency also depends on the ambient temperature. A larva hatches from the egg after about 1 or 2 days. There are 4 larval stages or instars before the pupal stage. The duration of each aquatic stage depends to large extent on temperature. The survival or longevity of the adult female depends on humidity and temperature.

1.3 Malaria endemicity and transmission intensity

According to the World Health Organization's Terminology of Malaria and Malaria Eradication (WHO 1963), malaria is described as endemic "when there is a measurable incidence both of cases and of natural transmission over a succession of years." Based on definitions formulated in the 1950s, malaria endemic areas have been classified according to spleen and parasite rates (WHO 1963; Snow and Gilles 2002).

Classification of malaria endemicity

The four levels of endemicity, in increasing order of transmission intensity, include: hypoendemic, mesoendemic, hyperendemic and holoendemic malaria.

Hypoendemic areas. These are areas with very little malaria transmission. The spleen and parasite rates usually do not exceed 10% in children aged 2-9 years. Due to the low risk of infection, most of the populations in these areas lack effective immunity against the disease.

Mesoendemic areas. These are areas with moderate transmission. Spleen and parasite rates range between 11% and 50% in children aged 2-9 years.

Hyperendemic areas. These areas have intense seasonal transmission but not sufficient enough for a very high proportion of the population to develop protective immunity. Spleen and parasite rates are between 51% and 75% in children aged 2-9 years. Adult spleen rates are usually high (>25%).

Holoendemic areas. These have perennial, intense transmission resulting in a considerable degree of immunity outside early childhood. Spleen rates are over 75% in children 2-9 years but low in adults. Parasite rates are over 75% among infants 0-11 months.

Macdonald suggested a more general classification of areas into two extremes of endemicity levels referred to as "stable" and "unstable" based on the intensity of transmission (MacDonald 1957). This classification integrates various epidemiological factors and can be used to broadly characterize transmission in malaria receptive areas. Areas with unstable malaria are mainly those with low or moderate transmission intensity, i.e. hypoendemic or mesoendemic areas. These can be affected by severe epidemics, often as the result of slight changes in environmental conditions conducive for vector breeding and survival as well as parasite development within the vector.

Transmission intensity and epidemic malaria

Epidemic malaria has been defined as "an acute exacerbation of disease out of proportion to the normal to which the community is subject" (MacDonald 1957). An increase in incidence may or may not be labelled "epidemic" depending on the magnitude of the excess of cases, the rate at which the excess develops, and interpretation of previous data from which to calculate the "expected" (Molineaux 1988).

In order to illustrate the volatile conditions prevailing in areas of unstable malaria, it would be necessary to first consider different approaches of measuring intensity and simulate the dynamics of transmission using some of these approaches. Five interrelated measures of intensity have been used in the study of malaria transmission (Molineaux 1988): (a) the incidence rate (number of new infections occurring in a given population unit); (b) the prevalence rate (fraction of a population infected at a given point in time); (c) the entomological inoculation rate (EIR) (number of infective mosquito bites received per person per time unit); (d) the vectorial capacity (C) (potential number of secondary cases originating per day from a primary case, assuming that the population is and remains fully susceptible); and (e) the basic reproduction number (R_0) (potential number of secondary cases originating from one primary case, assuming that the population is and remains fully susceptible; R_0 can be also expressed as C multiplied by the number of days a case remains infectious, which is the reciprocal of the recovery rate).

The vectorial capacity is an index that can also be considered as the capacity of a vector population to disseminate malaria in terms of the potential number of secondary inoculations originating per day from an infective person. Based on Macdonald's expression for the basic reproduction number (MacDonald 1957), the formula for the vectorial capacity (C) was given as follows by Garret-Jones (Garret-Jones 1964):

$$C = \frac{ma^2 p^n}{-\log_e p} \tag{1.1}$$

where m = density of vectors in relation to humans, a = number of blood meals taken on human per vector per day, p = daily survival probability (or proportion of vectors surviving per day), and n = incubation period in the vector or the length of the sporogonic cycle in days.

According to Ronald Ross's model, the human population can be divided into positive and negative fractions y and $1-y$, respectively (Molineaux 1985). The negatives become positive at a rate which is the product of the

fraction positive multiplied by a contact rate which is equivalent to C; and the positives become negative at a constant rate which is equivalent to the recovery rate per unit time (r). The model can be represented as follows:

$$y_{t+1} = y_t + y_t C(1 - y_t) - r y_t \qquad (1.2)$$

where, y_t = proportion of positives in the human population at time t and C and r are as described above. Assuming that the situation is in equilibrium, Equation 1.2 can be used to derive a formula for y as a function of C (Molineaux 1985). At equilibrium, $y_{t+1} = y_t$ and the added and subtracted terms should be equal; i.e. $y_t C(1 - y_t) = r y_t$. After dividing both sides by y_t, re-arranging the equation, and dropping the time subscript, we finally get:

$$y = 1 - \frac{r}{C} \qquad (1.3)$$

The endemic level y reaches 0 for $C = r$. As $C = rR_0$, by substitution, we can also describe y as a function of R_0:

$$y = 1 - \frac{1}{R_0} \qquad (1.4)$$

The relationship shown in Equation 1.4 is given in Figure 1.2. The endemic level (or prevalence) reaches zero for $R_0 = 1$. Malaria can be endemic only if R_0 is greater than 1. Close to this threshold, a small change in the equilibrium conditions produces a large change in the prevalence rate; far above the threshold, large changes in C or R_0 produce little or no change in the prevalence rate. Close to the threshold malaria is naturally unstable, and there is a risk of epidemics; far above the threshold it is naturally stable.

High endemicity levels characterize stable malaria. Fluctuations in incidence other than normal seasonal changes are not likely to be marked and epidemics are very unlikely to occur. The adult human populations in areas with stable malaria usually show a high level of immunity to malaria, and therefore only children are often at risk of severe disease and death due to malaria. Effects of changes in weather conditions (e.g. temperature) have little or no effect on transmission.

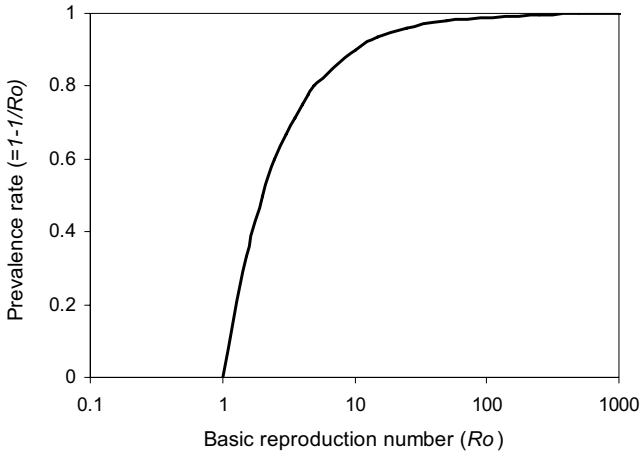

Figure 1.2 The relationship between the prevalence rate of malaria (y) and the basic reproduction number (R_0), based on Ross's malaria model (Molineaux 1988) (putting r = 0.002).

In contrast, areas with unstable malaria have low to moderate transmission. Fluctuations in incidence are likely to be very marked. Slight changes in transmission factors can lead to major epidemics. All age groups are affected by the disease due to low level of immunity as a result of fluctuation in transmission or low intensity of transmission.

In practice, however, there are several situations which cannot easily fit into these two broad classes, and thus it would be useful to consider a continuum of transmission situations. For example, in the unstable type, there are areas with highly seasonal but intensive transmission with more or less predictable pattern each year associated with occasionally explosive epidemics, and areas characterized with highly seasonal and very little or no transmission for several years. Areas with intense seasonal transmission can sometimes also be affected by true epidemics followed by successive abnormally dry periods (De Meillon 1950).

Geo-referenced highland areas affected by epidemics in the past have been identified in some countries in the Horn of Africa and Eastern Africa in order to study their altitudinal ranges and climate profiles in an attempt to

produce spatial risk maps (Cox *et al.* 1999). After extensive studies involving published and unpublished literature and topographic and climatic profiles of affected localities, a generally satisfactory method of characterizing areas with similar average annual climate has been used for risk classification. For example, in Kenya, areas where epidemics occurred in the past lie within an altitudinal range of 1,500—2,600 metres, with mean altitude of about 1,900 metres. However, mapping of epidemic risk using altitude alone was not satisfactory as it suggested that areas which have never been affected appeared to be at high risk. On the other hand, by using means and variance of annual rainfall and temperature profiles of the epidemic-affected localities produced better fitting risk maps (Cox *et al.* 1999). These maps are available for a number of countries with highland malaria at www.mara.org.za and www.himal.uk.net.

1.4 Epidemics and their precipitating factors

The burden of epidemic malaria in Africa

African highlands have been frequently affected by malaria epidemics that had devastating mortality consequences among populations with little or no immunity to the disease. According to WHO and UNICEF sources, an estimated 110 million people are at risk of malaria epidemics in Africa and 110,000 of these die of the disease each year (WHO/UNICEF 2003). Others attribute 12 million malaria episodes and 155,000—310,000 malaria deaths to epidemics in the absence of timely control measures (Worrall *et al.* 2004). At times, a single large-scale epidemic can cause very high mortality rates among affected populations. As an example, a major epidemic in Ethiopia in 1958 resulted in an estimated 3 million cases and 150,000 deaths within a 6 month period (Fontaine *et al.* 1961). Major epidemics have been reported in the past two decades from several African countries including Ethiopia, Kenya, Uganda, Zimbabwe, Botswana, Mozambique, Madagascar, Swaziland and South Africa (Nájera *et al.* 1998).

In areas with seasonal malaria, epidemics usually occur during the main transmission season, super-imposed over the normal seasonal increase (Garnham 1948). This phenomenon makes early detection of abnormal situations difficult. Malaria epidemics have also affected normally non-malarious highlands (as the result of abnormal increase in temperature) (Freeman and Bradley 1996), drought affected areas (when vectors breed in intermittent streams) (van der Hoek *et al.* 1997; Nájera *et al.* 1998), and arid lowlands (following abnormally high rainfall or flooding) (Brown *et al.* 1998).

Typology of epidemics

It is essential to characterize epidemics and to study their usual causes to design strategies for prevention and control. This would help in determining the appropriate early warning/surveillance and response systems that suit the particular epidemiological situations. The following epidemic types have been broadly identified based on disturbance patterns of equilibrium conditions (Nájera *et al.* 1998; Nájera 1999): (a) Epidemics that follow temporary disturbance of a stable hypoendemic equilibrium, which would eventually return to the previous endemicity level; (b) Epidemics resulting from major changes in the eco-epidemiological system, which result in a shift towards a new equilibrium; and (c) Epidemics that follow interruptions of control measures which had kept malaria in a "controlled" equilibrium.

There are several factors leading to the various types of epidemics. Increased vectorial capacity (due to natural or man-made causes), immigration of infectives to receptive areas, immigration of non-immunes to malarious areas, and drug resistance have been identified as the major epidemic precipitating factors (Molineaux 1988). Probably the least predictable of these is the increase in vectorial capacity due to changes in weather conditions, mainly resulting in the first type of epidemics affecting areas with low endemicity. For example, excess or deficit rainfall and increased temperature may increase vector emergence as availability of breeding places may increase. Inappropriate water management in irrigation schemes and deforestation also increase the vectorial capacity through increased availability of breeding sites. Deterioration of malaria control operations in the 1980s and 1990s and resistance of the parasites to drugs may have also contributed to increase of malaria in many areas, leading to the second type of epidemics, in which some of these areas have attained a higher equilibrium of transmission. Malaria has established itself in several highland areas which were previously considered non-malarious due to absence of transmission for several years. Epidemics resulting from interruption of previously well-managed control programmes have also affected some countries. In Madagascar, deterioration of malaria control activities has contributed to a major epidemic in 1987-88 (Mouchet *et al.* 1998).

El Niño Southern Oscillation and epidemics

Studies have shown the existence of a strong relationship between El Niño and malaria epidemics in different parts of the world. El Niño is a periodic climatic phenomenon that affects weather patterns in many areas around the world and is associated with warmer than average sea surface temperature

(SST) in the eastern equatorial Pacific Ocean. Epidemics were shown to be more prevalent in a year with a wet monsoon following a dry Niño year during the period 1868-1943 in Sri Lanka (Bouma and van der Kaay 1996). The same relationships have been shown to exist in Columbia, where malaria cases increased by 17% during an El Niño year and by 35% in post-El Niño year (Bouma *et al.* 1997). Based on these observations, it was proposed that such El Niño-malaria relationship can be used to predict high- and low-risk years for malaria in Columbia. In Venezuela, a study using data between 1975 and 1995 showed that malaria mortality and morbidity increased by more than 36% in post-El Niño years (Bouma and Dye 1997). In Uganda, abnormally high rainfall caused by El Niño in 1997 resulted in a severe epidemic (Kilian *et al.* 1999). A number of published findings have appeared during the last five years on possible causes of both short- and long-term increases in malaria episodes in areas with unstable transmission. More reports have continued to confirm the association of epidemic malaria with El Niño events in many parts of the world. As an example, in Columbia, researchers have analyzed malaria data for the period 1980-1997 to present evidence that the El Niño phenomenon intensifies the annual seasonal malaria transmission cycle (Poveda *et al.* 2001). Several reports have already produced consistent findings regarding the association between El Niño and malaria in the coastal regions of Venezuela and Columbia (Kovats *et al.* 2003).

Effects of climatic factors

Temperature affects malaria transmission in various ways (Craig *et al.* 1999). An increase in temperature results in shortened sporogonic period of the *Plasmodium* parasite within the vector up to about 30^{o}C. Mean daily temperatures above 30 ^{o}C will have a negative impact on the survival of the vector. On the other hand, increased temperature is also known to accelerate the development period of the aquatic stages of the vector.

The effect of temperature on duration of the sporogonic cycle in days (n) has been studied and quantified (Detinova 1962; Molineaux 1988). For *P. falciparum*, the relationship between n and mean temperature t in degrees Celsius is given as:

$$n = \frac{T}{t - t_{\min}} \qquad t_{\min} < t < 30 \qquad (1.5)$$

where T = 105, 111 and 144 for *P. vivax*, *P. falciparum* and *P. malariae* respectively, and $t_{\min}$ = 14.5 for *P. vivax*, 16 for *P. falciparum* and *P.*

malariae. Shortening of the sporogonic period as the result of increase in temperature up to 30°C leads to increased transmission as the parasite is more likely to attain an infective stage before the vector dies. If we denote the probability of the vector's survival through one day as p, then the probability of survival of the vector through the sporogonic period n would be p^n.

Analysis of 76 years of data from Zimbabwe has shown that higher than average mean September temperatures were associated with an increase in the severity of malaria in the following year (Freeman and Bradley 1996). Studies in Madagascar have also indicated that minimum temperatures during 2 months at the start of the transmission season (when there is a high human-vector contact) can account for most of the variability between years (Bouma 2003).

In the semi-arid or arid lowlands, heavy rain or floods can cause a major outbreak of malaria, especially in areas in the vicinity of large rivers. Such an outbreak has affected the low-lying semi-arid areas in north-eastern Kenya in 1998 following a major rainfall and floods (Brown *et al.* 1998). Spatial and temporal variations in rainfall determine the nature and scale of malaria transmission in highland areas. Abnormal rainfall events have been shown to precipitate malaria epidemics even in wetter areas—as evidenced by epidemics in Uganda, Kenya and Ethiopia (Cox *et al.* 1999). The effect of rainfall is inherently linked to that of humidity, which has a particularly significant effect on the longevity of adult vectors. In Uganda, rainfall during and following the 1997 El Niño was much higher than normal, and rainfall anomaly (difference from the mean) was positively correlated with vector density one month later, and it was concluded that heavier than normal rainfall associated with El Niño may have initiated the epidemics (Kilian *et al.* 1999; Lindblade *et al.* 1999). In Wajir, an arid area in north-western Kenya, it has been shown that it takes three months before the malaria incidence reaches a peak following a significant rainfall (Hay *et al.* 2001). This shows that it is straightforward to use rainfall alone in epidemic early warning. A remote sensing system already in place for famine early warning can be used for monitoring rainfall anomalies for malaria epidemic surveillance in such areas. The data is available in public domain on the Internet in near real-time at the Africa Data Dissemination Service (ADDS) web site (http://igskmncnwb015.cr.usgs.gov/adds/).

Studies on the effects of relative humidity (RH) on malaria vectors are limited. A laboratory-controlled study has shown that the maximum longevity of *A. culcifacies* in India was recorded between 60% and 80%, indicating that both low and excess humidity is detrimental to the vector especially at high temperatures (Pal 1943). Longevity was found to depend on both temperature and RH and their interaction. There is also interaction with rainfall and this

indicates the complex relationship existing among the three meteorological factors as well as between these factors and malaria and malaria vectors.

During the first two months of 1998, an epidemic affected the highlands of south-western Uganda which have normally low or moderate transmission. The increase in *P. falciparum* malaria in these highlands was attributed to the increased and prolonged rains in the last quarter of 1997 caused by El Niño Southern Oscillation (Kilian *et al.* 1999). A close correlation between peak of rainfall and peak of malaria incidence was observed with a lag of 2-3 months between them.

In Sri Lanka, temperature and relative humidity are favourable for malaria transmission throughout the year. Failure of the monsoon rains reduced rivers and streams in the wet zone of the country to stagnant pools of water which became ideal breeding grounds for *A. culcifacies* and caused two major epidemics in 1934-35 and 1967-68 (van der Hoek *et al.* 1997). In the dry zone, seasonal peaks in malaria occur 2 months after the peaks of rainfall. Previously, it was thought that rainfall could be used for the forecast of abnormal incidence, but this study indicates that the relationship between higher than average seasonal rainfall and higher than average seasonal malaria incidence was not very strong (van der Hoek *et al.* 1997). For example, rainfall immediately before and during the 1986-87 epidemic was within the normal limits. The relationship between rainfall and malaria has been confounded by environmental changes, population movements and changes in malaria control measures. Thus it was concluded that monitoring rainfall alone is insufficient for malaria early warning in dry zones of Sri Lanka, and early detection of increased incidence remains the best warning.

Man-made factors

Land use changes have taken place in the highlands in East Africa during the last several decades. The gradual increase and extension of malaria into the highlands of Kenya is believed to be due to a multitude of factors, including development activities such as agriculture, expansion of transportation networks, increased movement of populations, and deforestation (Garnham 1948). In Kericho, tea-growing highland area in Kenya, climate variables were found to explain seasonal patterns but inter-annual variations indicated the existence of a cyclical behaviour probably related to parasite and host population dynamics (Hay *et al.* 2001). It was suggested that early warning systems should incorporate such dynamics to deal with super-annual variations in epidemic risk. Extension of malaria into the highlands of Rwanda and Burundi has also been attributed to introduction of *A. gambiae* following swamp cultivation (Garnham 1948). A study carried out in the south-western

highlands of Uganda indicated that cultivation of natural swampy areas may have led to increased temperatures over the years, which may be responsible for elevated malaria transmission (Lindblade *et al.* 2000). Land use changes can alter the physical and chemical characteristics of mosquito breeding habitats. A study carried out in Kakamega forest in western Kenya (elevation 1,500-1,700 metres) has indicated that the survivorship of *A. gambiae* larvae was dramatically reduced in forest habitats compared to habitats fully exposed to sunlight, suggesting that deforestation facilitates malaria transmission in the highlands. The average daily water temperature of the open habitats is also more than 3 ^{o}C higher than in the forest habitats (Tuno *et al.* 2005). Development activities that would result in ecological changes can cause increases in malaria transmission. In a study carried out in hypoendemic highlands of northern Ethiopia (1,800-2,225 metres) where small dams have been constructed for agricultural purpose, it was found that incidence of malaria in children in villages within 3 kilometres of the dams was significantly higher compared to those 8-10 kilometres away from the dams (Ghebreyesus *et al.* 1999). Brick-making, an important economic activity in western Kenya, has been linked to increased vector densities (Carlson *et al.* 2004).

1.5 Epidemic early warning, detection and response

Early warning signals could help health services to take targeted and specific preventive measures prior to the onset of epidemics, and/or to take timely control measures. Malaria epidemic early warning is based on monitoring transmission risk indicators used to predict timing of an increase (such as abnormal weather conditions), and population vulnerability indicators used to predict severity of impact (such as loss of immunity due to recent history of low transmission) (Thomson and Connor 2001). Prediction of malaria epidemics using such factors can give lead-times of weeks to months, during which other surveillance activities can be enhanced and preventive and control measures targeting specific areas planned and implemented.

Epidemic early detection involves recognizing the beginning of an epidemic situation by measuring changes in local disease incidence. Although this surveillance mechanism offers little lead-time (days to weeks) for preparation and implementation of preventive measures, it can lead to a rapid and effective response to avert or reduce peak morbidity and mortality.

Disease surveillance for epidemic early detection

Disease surveillance and epidemic preparedness and response are among the priority areas identified under the plan of action adopted by African leaders at the Abuja Summit in April 2000 (RBM 2000). The recommended approaches and activities include: (a) strengthening health information systems to ensure reliable reporting of malaria cases and deaths as part of the integrated disease surveillance system; (b) providing health information to health workers and policy makers for appropriate decision-making; (c) establishing an effective epidemic preparedness and response capability to detect and contain outbreaks as rapidly as possible; and (d) establishing an effective system to alert malaria control authorities and policy makers in other relevant sectors of new development projects, population movements, as well as environmental and climatic changes that could impact the malaria situation. Indicators selected for monitoring progress of epidemic preparedness and response include: per cent of malaria epidemics detected within 2 weeks of onset; and per cent of malaria epidemics properly controlled within 2 weeks of onset.

The main goal of setting up an epidemic surveillance system is to build capacity of the health services to take timely preparedness, preventive and/or control measures. In most epidemic-prone African countries, the surveillance system has been weak, inefficient or incapable of detecting an abnormal malaria transmission at its early stage. This has been due to several factors including: lack of an efficient and standard system of reporting surveillance data; lack of a specific and sensitive outbreak detection algorithm; a long time lag between observed incidence at health facilities and transmission of data mainly as the result of monthly reporting systems; under-utilization of data at points of collection or at levels where action can be taken on time, this being due to traditionally centralized systems of surveillance; lack of the necessary knowledge and skills of local staff on the importance of surveillance data; manual processing of data because of a lack of the necessary computing equipment; and a lack of communication facilities between peripheral health services, districts and the central level.

The health service reform during the last two decades to decentralize decision-making appears to have created the necessary platform for dealing with some of these problems. However, the disease surveillance systems in many countries still heavily rely on support from the central level.

In eastern African countries, it is only during the last five years that Ministries of Health began rolling out their disease surveillance services to district levels. In many cases, such decentralized systems are still at their immature stages and a substantial overlap of activities exists within an unclear system for handling emergencies. Furthermore, the information system is not

well developed to enable districts to maintain effective, computerized database systems and to carry out the necessary analyses of the data they collect and use the results for action. Outbreaks used to be detected in many areas at or near their peak, by which time prevention or control measures have little impact on morbidity and mortality.

Geographic information systems

The use of geographic information systems (GIS) in studies involving the spatial distribution and intensity of transmission has been given a significant attention since the last decade mainly as the result of the so-called MARA/ARMA Collaboration Project, which was initiated by researchers across Africa to provide an atlas of malaria for the whole continent. The atlas contains relevant information for targeted implementation of malaria control based on parameters such as transmission intensity (www.arma.org.za). The malaria transmission intensity map was prepared mainly based on climatic determinants (Craig *et al.* 1999).

Initially as part of the MARA/ARMA Collaboration, the Highland Malaria Project (HIMAL) was initiated to focus on epidemic malaria in the highlands. Epidemiological and climatic data were used to produce spatial epidemic risk maps for a number of countries including Ethiopia, Kenya, Tanzania and Uganda (Cox *et al.* 1999). These maps are useful for countries/districts to delineate areas at high, moderate or low epidemic risk so they may establish selective monitoring of epidemiological data in representative sites. However, temporal and dynamic risk maps are required to delimit areas for preventive or control measures to deal with actual epidemic events. Unless there is some form of dynamic risk models that can be continuously updated, countries still lack sufficient basis to take preventive measures, some of which are relatively expensive.

Development of temporal risk maps for epidemic risk monitoring is a major research undertaking which involves detailed studies of epidemic precipitating factors. Such studies will be useful to develop models that may describe the genesis of epidemic malaria in different areas and situations, especially in highlands or highland fringes where slight changes in precipitating factors such as elevated temperature might result in severe outbreaks. Forecasting models will therefore be the basis for the development of temporal risk maps.

However, the task of developing epidemic early warning methods has proved difficult especially for highland areas, and there are still no reliable forecast systems other than general warnings for large geographic areas following abnormal weather conditions.

Various attempts have been made to use climatic/environmental, remote sensing, entomological and morbidity data in epidemic prediction or early warning (Cullen *et al.* 1984; Connor *et al.* 1998; Lindblade *et al.* 2000; Hay *et al.* 2001; Thomson and Connor 2001; Rogers *et al.* 2002). Onori and Grab have tested the theoretical impact of various factors that influence the level of transmission in epidemic-prone areas (Onori and Grab 1980). They concluded that inoculation rate is extremely sensitive to slight changes in survival rate of the vector and the period of the sporogonic cycle. Both these factors are influenced by changes in temperature, rainfall and humidity. Careful monitoring of meteorological factors would theoretically produce good early warning of epidemics. However, the accurate quantification of the effects of these variables requires more rigorous research.

It is important to detect abnormal incidence well before it develops into a severe epidemic, in order to initiate timely prevention or control measures. Different techniques of recognition and early detection of malaria epidemics have been used, all based on the definition of the normal (or expected) incidence for a particular area and point in time.

A method proposed by Cullen (Cullen *et al.* 1984) uses the previous five years of data to construct incidence profile for an average year. The alert threshold for each month is then determined as the mean plus 2 times the standard deviation. The WHO advocate the use of an upper normal limit—the third quartile (Hay *et al.* 2002). The Centres for Disease Control and Prevention (CDC) have developed a method which is based on the construction of an average for a particular month by using incidence for that month, the previous month and the following month during the baseline years for detecting epidemics (CDC 1989; Stroup *et al.* 1989; Stroup *et al.* 1993). For example, the expected number of cases for May 2003 would be derived from the average of April, May and June cases from 1998 to 2002, inclusive. A ratio of present to past cases is calculated and then presented as a current-to-past history graph, with values greater than one representing disease increases.

The weak surveillance/information systems in many countries have led to delayed responses to epidemics. In many cases, compiled monthly morbidity data are of not much use for epidemic detection, and thus weekly data collection and analysis is encouraged to identify early abnormal situations. In many health facilities, there is insufficient baseline data to establish the "normal" levels for each week of the year upon which the system for detection of abnormal situations is based. The quality as well as quantity of the baseline data determines what is considered 'normal'. Long-term trends due to treatment failures, population increase, etc. are also likely to affect the calculation of the 'normal'. Due to these and other difficulties, the different

epidemic recognition/early detection methods have limited use. Improved systems are required to identify truly abnormal conditions.

Following surveillance frameworks developed with national malaria control programmes and district health management teams in Eastern African countries, the Highland Malaria Project (HIMAL) has been developing systems for early warning and detection in the East African highlands focusing on building local capacity in epidemic management. This collaborative research project was launched in 2001 as part of the Gates Malaria Partnership in London School of Hygiene and Tropical Medicine (LSHTM). The project's goals include creating and testing functional systems for epidemic early warning and detection incorporating district-level sentinel surveillance and predictive modelling using environmental data, remote sensing (RS) and GIS. Technical feasibility of early warning and early detection is evaluated to develop practical recommendations for affected countries. Meteorological, entomological, parasitological and clinical data are collected simultaneously on a continuous basis in four districts in Kenya and Uganda. A computer-based automated analysis of surveillance data has been established in the pilot districts (www.himal.uk.net).

Epidemic response

Response to malaria epidemics should be as prompt as possible. The recommended epidemic control measures include mass fever treatment, management of severe cases and in the case of active and continuing transmission, vector control measures, in particular indoor residual spraying (IRS) with an effective insecticide (WHO 2004). However, resistance against traditionally inexpensive drugs such as chloroquine and SP by *P. falciparum* has become a major obstacle in effectively using mass fever treatment due to costs of more effective drugs such as ACTs. The lack of effective and area-specific early warning or prediction systems has also been a major impediment to the use of vector control measures such as IRS for prevention purposes well in advance of epidemic events.

Longer term increase of malaria in the highlands in recent years might have non-climatic causes, including drug resistance of the parasite, with or without climatic causes, and it is essential to study the effects of these factors for more conclusive evidence. Nevertheless, current evidence appears to show that climate variability, resulting from climate change or El Niño conditions, plays an important role in causing short-term, but at times devastating, epidemics of the disease in these areas. Adaptation measures to reduce the consequences of epidemic malaria include developing effective surveillance systems and methods of prediction and early response. More research is

needed to fully understand the processes that trigger epidemic malaria in the highlands to develop robust early warning systems.

1.6 Aim and research questions of the thesis

The general aims of the thesis are to (i) understand the effects of environmental risk factors for malaria epidemics in countries in the Horn of Africa and Eastern Africa, (ii) to develop and test malaria early warning and early detection systems in these areas and (iii) to discuss the implications for prevention and control.

The thesis will try to address these aims through answering the following research questions:

1. What is the state of the art of malaria epidemic early warning and the potential use of computer-based sentinel surveillance for early detection?
2. How helpful are time series methods in forecasting malaria epidemics?
3. How is variation in epidemic risk linked with environmental factors?
4. Is biological reasoning useful in statistical modelling of environmental data for predicting malaria incidence?
5. How should malaria epidemic prevention and control be linked to epidemic risk assessments and what are the challenges?

1.7 Structure of the thesis

This thesis focuses on: (a) epidemiological research to understand malaria epidemic precipitating factors and on the use of these factors in developing early warning systems in areas with unstable transmission; (b) research outputs of the performance of some time series methods with potential of forecasting incidence based on historical morbidity patterns, (c) operational studies to develop effective surveillance systems and algorithms for epidemic detection at their early stages; and (d) discussions on challenges and opportunities related to available epidemic response options within the context of affected countries. A special emphasis has been given to epidemics in the highlands of Ethiopia, Kenya and Uganda.

Research question 1 on the state of the art of epidemic early warning is addressed in Chapter 2. Research question 2 on time series is dealt with in Chapter 3. The focus of Chapter 4 will be research question 3 on the link of environmental factors with epidemic risk, followed by Chapter 5 which

addresses the use of biological reasoning in statistical modelling of environmental data for predicting malaria incidence (research question 4). Research question 5 on the links between epidemic risk assessments and prevention and control measures and the associated challenges will be addressed in Chapter 6. Finally, the overall synthesis of the research questions and outcomes of the studies will be discussed in Chapter 7 with some related additional findings, within the wider context of other (past and on-going) studies in malaria epidemic management.

2

Malaria epidemic early warning and detection in African highlands

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2.1 Summary

Malaria epidemics have long been known to recur in the African highlands. Efforts to develop systems of early warning and detection for epidemics are outlined here with special emphasis on the Highland Malaria Project (HIMAL). This project has been conducting research on the operational implementation of a district-based surveillance and epidemic-monitoring system using a network of sentinel sites in four pilot districts of Kenya and Uganda. The potential use of weather monitoring as well as disease surveillance for effective early warning is being investigated.

2.2 Introduction

The African highlands have been frequently affected by malaria epidemics, often with devastating morbidity and mortality consequences among populations with little or no immunity to the disease Garnham 1948; Lindsay & Martens 1998; Cox *et al.* 1999; http://www.lshtm.ac.uk/dcvbu/himal/Documents.html). Epidemic malaria has been defined as 'an acute exacerbation of disease out of proportion to the normal to which the community is subject' (MacDonald 1957). It is estimated that 110 million people are at risk of malaria epidemics in Africa and 110,000 of these die of the disease each year (WHO/UNICEF 2003). In the past decade, epidemics have been reported from several areas including Ethiopia, Kenya, Uganda, Zimbabwe, Botswana, Mozambique, Madagascar, Swaziland and South Africa (Loevinsohn 1994; Freeman and Bradley 1996; Malakooti *et al.* 1998; Mouchet 1998; Nájera *et al.* 1998; Kilian *et al.* 1999; Lindblade *et al.* 1999; Hay *et al.* 2003; Abeku *et al.* 2004). Early warning and detection systems are needed in these and other areas at risk, to reduce or avert the negative public health and economic impacts of epidemics (Nájera 1999; Thomson and Connor 2001; WHO/RBM 2001). Reasonably accurate warning signals could help health services to take targeted and specific preventive measures before the onset of epidemics.

2.3 Terminology

It is important to distinguish between different terminologies that have been used to describe activities for monitoring epidemic risk, including long-range epidemic forecasting, malaria epidemic early warning and epidemic early detection. These activities are sequential, complementary and have decreasing lead times with increasing accuracy (Cox *et al.* 1999; WHO/RBM 2001; Kuhn *et al.* 2004; WHO 2004) (see: http://www.int/globalchange/publications/oeh0401/en/index.html and http://mosquito.who.int/docs/BamforthLeysinreport.pdf).

Long-range epidemic forecasting based on climate forecasting and El Niño Southern Oscillation indices has been proposed for the broad prediction of epidemic risk months in advance over large geographical areas. This allows time for resource allocation and general preparedness for an eventuality of an epidemic in the coming malaria season (Bouma and van der Kaay 1996; Bouma *et al.* 1997; WHO 2004).

Malaria epidemic early warning is based on monitoring transmission risk indicators used to predict timing of an increase (such as abnormal rainfall and/or temperature), and population vulnerability indicators used to predict severity of impact (such as poor nutritional status, drug resistance, loss of immunity due to recent history of low transmission or high incidence of HIV/AIDS) (Nájera 1999; WHO/RBM 2001; WHO 2004). Prediction of malaria epidemics using such factors can give lead times of weeks to months, during which other surveillance activities can be enhanced, and preventive and control measures targeting specific areas can be planned and implemented.

Epidemic early detection involves recognizing the beginning of an epidemic situation by measuring changes in local disease incidence. Although this surveillance mechanism offers little lead time (days to weeks) for preparation and implementation of preventive measures, it can lead to a rapid and effective response to avert or reduce peak morbidity and mortality (WHO/RBM 2001; WHO 2004).

2.4 The Highland Malaria Project (HIMAL)

HIMAL (http://www.himal.uk.net) is a continuation of work that produced spatial epidemic risk maps in the late 1990s as part of the Mapping Malaria Risk in Africa (MARA) collaboration (Cox *et al.* 1999). The distribution of malaria epidemic risk in the highlands of East Africa was modelled on the basis of climate parameters and known historical distribution of epidemics. Results suggested that highland epidemics tend to occur within defined altitudinal ranges, which vary by country primarily as a function of latitude. However, efforts to map epidemic risk on the basis of these ranges proved unsuccessful and demonstrated that altitude on its own is a poor indicator of the likelihood of epidemics. More-reliable estimates of epidemic risk could be obtained using representative climatological profiles for epidemic-prone localities in each country and by classifying risk according to how closely annual climate patterns matched those of known epidemic-prone areas (Cox *et al.* 1999).

The current phase of the HIMAL project began in 2001, and aims to create and test functional systems for malaria early warning and early detection, incorporating district-level surveillance and predictive modelling using environmental data, remote sensing (RS) and geographical information systems (GIS). As well as addressing the technical feasibility of early warning, the project will evaluate the current prospects for implementation from an institutional perspective, and will develop recommendations for ongoing data collection and proactive epidemic management strategies.

2.5 New approaches to epidemic monitoring

A new surveillance system, introduced in October 2002, comprises a network of 20 sentinel health facilities in four pilot districts: North Nandi and Gucha in Kenya, and Kabale and Rukungiri in Uganda. Geographically, these districts are partly or wholly prone to epidemics. It is extremely important to detect abnormal incidence in such areas as early as possible to initiate timely preventive and/or control measures. Disease surveillance systems in many developing countries, including those with unstable malaria, are usually based on monthly (and often irregular) reporting to the central authorities, and have resulted in delayed responses to epidemics (Hay *et al.* 2003). Monitoring morbidity data on a monthly basis is often of little practical use for epidemic detection because the temporal resolution does not allow an early response(Hay *et al.* 2003; Hay *et al.* 2003). Surveillance data from the sentinel sites within HIMAL are therefore reported to the District Health Management Team (DHMT) on a weekly basis.

Different techniques have been suggested for the determination of thresholds that are predictive of a dramatic and unexpected increase in future cases. Most of these techniques are based on the definition of the 'normal' (or expected) incidence for a particular area and point in time, with varying sensitivity and specificity (Cullen *et al.* 1984; CDC 1989; Stroup *et al.* 1993; Nájera *et al.* 1998; WHO/RBM 2001; Hay *et al.* 2002). Application of currently recommended epidemic detection algorithms in epidemic-prone settings has demonstrated that they lack required sensitivity and specificity, and the need to develop robust and reliable approaches to detection remains a significant research issue (Hay *et al.* 2002).

Within HIMAL, a special database application is used at the district level for data entry and automated analysis, which includes a built-in incidence-monitoring system for detecting aberrations based on week- and area-specific levels of disease incidence assessed against a baseline period of seven or more years. The epidemic onset detection method being tested is a modification of the Salmonella Potential Outbreak Targeting System (SPOT) developed in Australia (Stern and Lightfoot 1999). Incidence in a sentinel health facility during a baseline period is de-trended (after log transformation) to minimize possible bias caused by events such as malaria endemicity equilibrium changes, population growth and establishment of new health facilities in the catchment area of sentinel sites. Furthermore, the Loess de-trending method (Cleveland 1979; Makridakis *et al.* 1998) is used to ensure that outliers and abnormally high incidences during the baseline period would not affect the trend line fitted to the data.

The de-trended series is then smoothed using the 4253H-Twice method (Velleman and Hoaglin 1981). The mean for each week and an overall standard deviation are then calculated from the de-trended and smoothed series. An anomaly measure — called the standardized departure — is calculated by dividing the difference between the observed (de-trended log) number of cases and the mean for the particular week number by the overall standard deviation of the baseline. This measure reflects deviation from normal, yet taking into account the variability within the baseline data. Both the values and the trend of the standardized departure during the 12 most recent weeks are used to assess the degree of aberration. Values around zero indicate normal incidence and those above 1 are tentatively considered abnormally high, especially if there has been an upward trend in the anomaly during the previous weeks (Figure 2.1).

Although a plot of the standardized departure gives an indication of the trend of incidence anomaly in several sites, it will also be necessary to use the site-specific incidence levels and to characterize objectively an epidemic situation for each area. Tentatively, an epidemic is flagged if weekly incidence exceeds both: (i) the week-specific mean plus one standard deviation (i.e. standardized departure value of 1); and (ii) the overall mean plus one standard deviation threshold. The week-specific expected values as well as the overall mean and standard deviation are dynamic and change over time depending on the underlying trend. A chart that allows visual inspection of weekly incidence together with the corresponding threshold values (Figure 2.2) is automatically generated by the database together with several other charts. This new epidemic detection method is explained further in Box 2.1.

The surveillance approach being piloted by the malaria control programmes in Uganda and Kenya builds upon, and compliments, the standard health-facility-centred model used in many Health Management Information Systems (HMIS). Key differences between these systems are listed in Box 2.2.

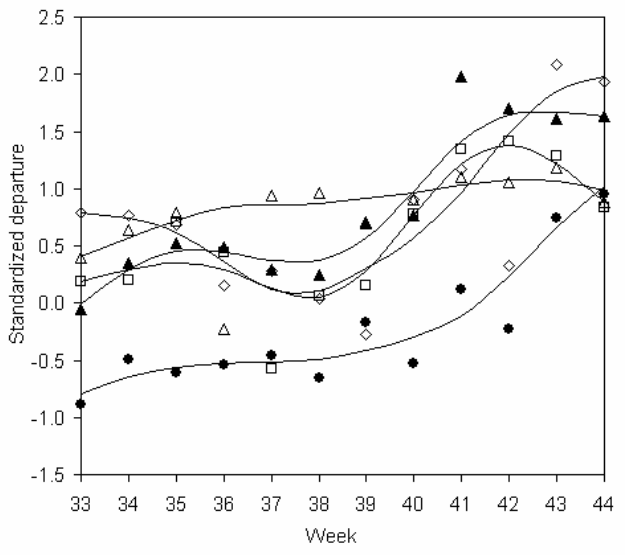

Figure 2.1 Standardized departure from expected number of clinical malaria outpatients during Week 33 to Week 44 of 2003, at five sentinel health centers in the Kabale District, Uganda. The weekly points indicate the actual standardized departure values for each sentinel site and the corresponding lines have been smoothed to aide interpretation. An epidemic could be detected at Week 41 in the sentinel sites (except Bufundi), using this automated output from the Highland Malaria Project (HIMAL) database. Both the weekly trend (as in Mparo during Week 38 to Week 41, for example) and the level of the standardized departure are used to determine a developing epidemic. (A more objective definition of an epidemic using threshold values is given in Box 2.1 and Figure 2.2.) Key: black circle, Bufundi; white triangle, Kitanga; white square, Mparo; white diamond, Buhara; black triangle, Bukinda.

Box 2.1 The Highland Malaria Project (HIMAL) epidemic detection system

To describe the epidemic detection algorithm, suppose X_t = weekly number of (clinical) malaria cases seen at a sentinel surveillance site at time t; $Y_t = Log_e(X_t + 1)$; $\overline{Y} =$ overall mean of the Y_t series during the baseline period (which increases in length over time, but excludes the last 12 weeks); $L_t =$ Loess trend line value at time t estimated from the Y_t series (Cleveland 1979; Makridakis et al. 1998); and $\overline{L} =$ overall mean of the Loess trend line values.

Then, the de-trended value corresponding to Y_t is calculated as $\hat{Y}_t = Y_t - L_t + \overline{L}$. 4253H-Twice smoothing (Velleman and Hoaglin 1981) is then applied to the de-trended series to generate a new series, with a value M_t at time t. E_{wt}, the expected value of $\hat{Y}_t$ for week w of the year at time t $(w = 1,2,...,52)$, is given by the mean of all M_t values for week w during the baseline years. Then, the standardized departure (D_t), the anomaly measure, is calculated as, $D_t = (\hat{Y}_t - E_{wt})/S$, where S is the overall standard deviation calculated from the de-trended and smoothed baseline series. D_t can be plotted for several sentinel sites in a single chart as shown in Figure 2.1.

Two threshold values (shown in Figure 2.2 plotted for each sentinel site separately with the original X_t series) are used to detect an epidemic (when both are exceeded). These are calculated in actual number of malaria cases after 're-trending' and back-transformation. The week-specific threshold for time t, $K_t = \exp(E_{wt} + L_t - \overline{L} + S) - 1$, whereas the overall mean plus one standard deviation threshold, $\overline{K}_t = \exp(\overline{Y} + L_t - \overline{L} + S) - 1$.

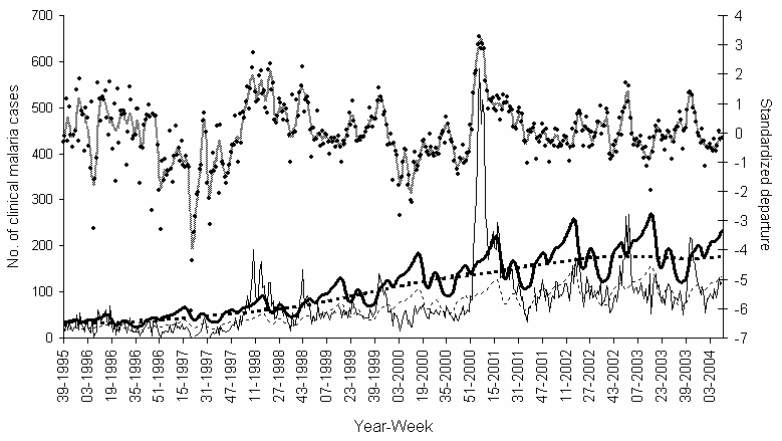

Figure 2.2 Historical morbidity pattern of clinical malaria between October 1995 and March 2004 at Mparo Health Centre, Kabale District, Uganda. The series shown are the observed number of cases (thin solid line), the expected number of cases (thin broken line), the week-specific mean plus one standard deviation threshold (thick solid line), the overall mean plus one standard deviation threshold (thick broken line), and the standardized departure values (black dots with gray line). An epidemic is tentatively defined when weekly incidence exceeds both threshold values. The baseline period is from Week 39 of 1995 to Week 38 of 2003.

2.6 Developing epidemic early warning systems

Various attempts have been made to use climatic/environmental, RS, entomological and morbidity data for epidemic forecasting (Cullen *et al.* 1984; Connor *et al.* 1998; Lindblade *et al.* 2000; Hay *et al.* 2001; Thomson and Connor 2001; Abeku *et al.* 2002; Rogers *et al.* 2002) , but the science is far from complete. HIMAL has created a unique opportunity to carry out detailed longitudinal studies to explore the associations between selected meteorological, entomological and morbidity variables as an empirical basis for developing and testing predictive models. The temporal and spatial resolutions of the prospective studies will allow modelling of the malaria transmission system in relation to the genesis of epidemics. Locality-specific weekly determination of indoor resting densities of *Anopheles* vectors, together with continuous parasitological confirmation of clinical malaria using

rapid diagnostic tests, weather monitoring and RS data, will provide a strong platform for detailed analysis and modelling.

Box 2.2. New surveillance approach for epidemic early detection

- The District Health Management Team (DHMT), rather than the Ministry of Health at the central level, is the focus for data collation, analysis and interpretation. Whether this decentralized approach is better suited to effective epidemic control than prevailing centralized approaches remains to be seen and needs to be evaluated rigorously.
- Data entry, organization and analysis, together with report generation, are all computer based.
- A weekly system of surveillance has been introduced. This facilitates assessment of the relative sensitivities and specificities of early detection systems based on monthly and weekly reporting. Data from individual health facilities are analyzed and interpreted before any data aggregation is carried out.
- The system makes efficient use of information from a small number of sentinel sites representing epidemic-prone geographical areas within a district, rather than attempting to monitor data from all health facilities.
- Historical morbidity patterns are used as the basis for monitoring anomalies within prospective data, and the trend in the baseline is taken into account in the definition of epidemic situations using an objective and automated early detection algorithm.
- The system incorporates a rapid dissemination mechanism for data, reports and feedback between sentinel sites, DHMT, the Ministry of Health and other relevant decision-making bodies, including district administrative authorities. In the case of a detected epidemic in one or more of the sentinel sites, the DHMT can rapidly look at incidence levels in other health facilities to delineate affected areas and select appropriate control measures, including mass or fever treatment and vector control.

A partnership established between HIMAL and the Epidemio Project of the European Space Agency (http://www.epidemio.info) will make available Earth Observation (EO) data for daily maximum and minimum land surface temperature at a spatial resolution of 5 km, whereas dekadal (10-day) rainfall estimates and normalized difference vegetation index (NDVI) data, which are available at a spatial resolution of 8 km from the Africa Data Dissemination Service (http://edcw2ks21.cr.usgs.gov/adds/), will also be utilized. EO data available in the public domain are limited with respect to both temporal and

spatial resolution. One task of HIMAL is to evaluate the implications of these constraints in relation to efforts to model malaria transmission.

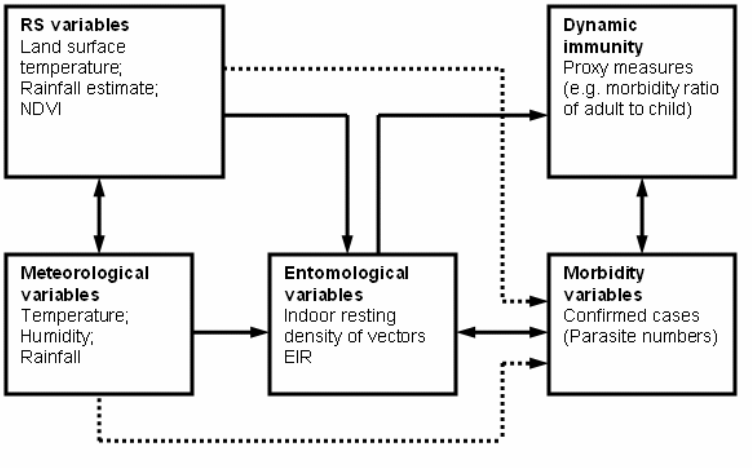

Figure 2.3. Epidemic-related factors and their relationships that are under investigation by the Highland Malaria Project. Prospective data are collected within the project to provide an empirical base for developing epidemic prediction models. Direct and indirect relationships between variables are represented by arrows with solid and broken lines, respectively. Although all indicated variables will be used in modelling transmission dynamics, meteorological (both ground and Earth Observation), in addition to morbidity data from sentinel health units, are variables that are most important for practical prediction. Abbreviations: EIR, entomological inoculation rate; NDVI, normalized difference vegetation index; RS, remote sensing.

The locality-specific longitudinal data with high temporal resolutions for meteorological, entomological and malaria morbidity variables will be used to shed light on the complex relationships between these factors, through combinations of statistical, analytical (mathematical) and/or simulation modelling approaches (Figure 2.3). A model reflecting biological relationships between meteorological and morbidity variables using retrospective data from Ethiopia, which includes rainfall two and three months earlier, mean minimum temperature of the previous month and *Plasmodium falciparum* case incidence during the previous month, has been used to study the weather–malaria

relationship and has indicated that a dynamic immunity mechanism is needed in prediction models (Abeku *et al.* 2004). Dynamic immunity might be incorporated in potential models through the use of proxy measures such as adult-to-child ratio of patients presenting at sentinel sites. In this respect, abnormally low incidence will also be monitored, as it might be a risk factor for future epidemics owing to the associated reduced immunity of the population.

2.7 Perspective

Further validation and refinement will be made to the epidemic detection techniques being implemented within HIMAL through detailed analysis of morbidity data and comparison of different algorithms to develop a reliable surveillance system. Better insights into the practical use of weather variables as predictors of epidemics are desirable. In the medium term, the use of EO and morbidity surveillance data (with or without ground meteorological data) will be investigated for spatial and temporal prediction of epidemic malaria, potentially removing the need for intermediate entomological variables. The use of EO data for scaling-up risk models without recourse to ground-based meteorological data will also be assessed. This work is expected to provide regular assessments of epidemic risk in affected areas at different lead times, to which uncertainty measures are progressively attached to assist the relevant authorities in making sound decisions for effective, long-term management of epidemic malaria.

Acknowledgements

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3

Forecasting malaria incidence from historical morbidity patterns in epidemic-prone areas of Ethiopia: a simple seasonal adjustment method performs best

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Tropical Medicine and International Health (2002) **7**, 851-857

3.1 Summary

The aim of this study was to assess the accuracy of different methods of forecasting malaria incidence from historical morbidity patterns in areas with unstable transmission. We tested five methods using incidence data reported from health facilities in 20 areas in central and north-western Ethiopia. The accuracy of each method was determined by calculating errors resulting from the difference between observed incidence and corresponding forecasts obtained for prediction intervals of up to 12 months. Simple seasonal adjustment methods outperformed a statistically more advanced autoregressive integrated moving average method. In particular, a seasonal adjustment method that uses mean deviation of the last three observations from expected seasonal values consistently produced the best forecasts. Using 3 years' observation to generate forecasts with this method gave lower errors than shorter or longer periods. Incidence during the rainy months of June–August was the most predictable with this method. Forecasts for the normally dry months, particularly December–February, were less accurate. The study shows the limitations of forecasting incidence from historical morbidity patterns alone, and indicates the need for improved epidemic early warning by incorporating external predictors such as meteorological factors.

3.2 Introduction

Malaria affects mainly children in highly endemic areas where adults have (partial) immunity to the disease. In contrast, in areas of low endemicity, the disease may affect all age groups. In such areas, changes in weather conditions may lead to major epidemics.

In Ethiopia, such epidemics have from time to time inflicted high mortality among the largely non-immune population. A well-documented major epidemic in 1958 resulted in an estimated 3 million cases of whom 150,000 died (Fontaine *et al.* 1961). Such a large-scale epidemic has been known to return at some irregular intervals of years; for example, during the 1980s and 1990s, severe epidemics were recorded in 1981, 1988, 1991, 1992 and 1998. It had not been possible to forecast any of these events, especially in highland areas that were normally considered non-malarious or had very low transmission. As an example, in 1988, a major epidemic affected most highland areas in the country following normal or below normal transmission the previous year (manuscript in preparation). A similar epidemic in 1998 resulted in high levels of mortality in highland areas where the disease had been absent for years.

In areas with unstable transmission, setting up systems for epidemic early warning has become essential. The quantification and use in early warning of the effect of epidemic-precipitating factors such as weather patterns has been difficult in epidemic-prone areas where slight changes might cause devastating epidemics. Currently there are efforts to develop early warning systems that use weather monitoring and climate forecasts and other factors (Thomson and Connor 2001). In some countries, epidemics have been associated with the occurrence of the weather phenomenon known as the El Niño (Bouma and van der Kaay 1996; Bouma and Dye 1997). While predicting El Niño years is not a simple task, even such predictions would be too global in nature to be useful as an early warning in specific areas. Moreover, there are variations in the magnitude and timing of the effects of El Niño on malaria incidence according to geographical conditions.

Specific forecasts of incidence would be helpful to local health services for appropriate preparedness and to take selective preventive measures in areas at risk of epidemics. In this study, we explore whether it would be possible to forecast malaria incidence from the patterns of historical morbidity data alone (without external predictors) while making use of the correlation between successive observations, and compare different methods of doing so in terms of the level of accuracy obtained. Our aim was to find out what

information can maximally be obtained from past morbidity trends and patterns which may be useful for prediction of future incidence levels, and to identify months or situations where additional information is needed most. We used monthly incidence data collected in areas with unstable transmission in Ethiopia.

3.3 Materials and methods

Study areas and data

We used historical monthly morbidity data from 20 areas in central and north-western Ethiopia (Table 3.1). Data sets from seven areas comprised microscopically confirmed *Plasmodium falciparum* cases seen at malaria laboratories. The data set from one area (Finote Selam) comprised combined monthly reports of *P. falciparum* cases from a number of health facilities reporting to the Sector Malaria Control Office. Data sets from the remaining 12 areas comprised unconfirmed clinical cases symptomatically diagnosed as malaria by trained health workers. We assume that fluctuations in the number of clinical malaria cases reflect proportional fluctuations in *P. falciparum* cases. There are *P. vivax* cases regularly reported in most areas of the country, but compared with *P. falciparum*, their number shows little seasonal fluctuation.

The monthly morbidity data has an approximately lognormal distribution, and therefore the analysis was based on log-transformed series. We calculated relative (log) incidence (RI) in order to bring morbidity data from all areas to the same scale. The RI for month t (denoted Y_t) was calculated as:

$$Y_t = \frac{\ln(Z_t)}{A}$$

where Z_t is the number of cases in month t and A is the overall mean of the log-transformed series used for forecasts. The back-transformed number of cases is thus: $Z_t = \exp(AY_t)$. The mean (A) differs for each series or sample.

Table 3.1 The 20 study areas with associated period and number of monthly observations used (*n*). The data used in the analysis include confirmed *Plasmodium falciparum* cases (areas 1–8) and clinically diagnosed malaria cases (areas 9–20).

No	Area/locality	Type of health facility*	Period	n
1	Bahir Dar (urban)	ML	Jul 90 – May 99	119
2	Finote Selam Sector	MDTPs	Oct 86 – Aug 95	107
3	Nazret (urban)	ML	Sep 94 – Mar 99	55
4	Nazret (rural)	ML	Sep 94 – Mar 99	55
5	Debre Zeit (urban)	ML	Sep 94 – May 99	57
6	Debre Zeit (rural)	ML	Sep 94 – May 99	57
7	Zway (urban)	ML	Nov 94 – Mar 99	53
8	Zway (rural)	ML	Nov 94 – Mar 99	53
9	Ambo Meda	HS	Mar 93 – Jan 99	71
10	Yifag	HS	Mar 93 – Jan 99	71
11	Chagni	HC	Jul 93 – Feb 99	68
12	Chireti	HS	Jul 93 – Feb 99	68
13	Chara	HS	Jul 93 – Feb 99	68
14	Dangila	HC	Jul 93 – Feb 99	68
15	Tamuha	HS	Jul 93 – Feb 99	68
16	Estie	HC	Mar 93 – Jan 99	71
17	Hamus Wenz	HS	Jul 92 – Jun 97	60
18	Debre Tabor	HC	Mar 93 – Jan 99	71
19	Wereta	HS	Jul 92 – May 98	71
20	Azena	HS	Jul 93 – Feb 99	68

*ML = malaria laboratory; MDTPs = malaria detection and treatment posts; HS = health station; HC = health centre.

Forecasting methods

The following methods were used to forecast RI m months in advance, i.e. to obtain the forecast for month $t+m$ (denoted $\hat{Y}_{t+m}$). The methods, ordered in degree of complexity, were compared in terms of their forecast accuracy.

Overall average
This simple method uses the mean of the observed RI values as forecast value for all future months. The mean on the RI scale obviously takes the value of 1:

$$\hat{Y}_{t+m} = 1$$

Seasonal average
This method uses the historical average of each particular calendar month as a forecast for the same month in the future. In other words, the average of all observed RI values during the same calendar month in previous years will be a forecast value for all similar months in the future:

$$\hat{Y}_{t+m} = A_{t+m}$$

Seasonal adjustment with last observation
In this method, the seasonal average was corrected using the deviation of the most recent observation from its expected seasonal value to generate forecasts for future months. The object was to capture incidence trend during the most recent months:

$$\hat{Y}_{t+m} = A_{t+m} + (Y_t - A_t)$$

Seasonal adjustment with last three observations
In this method, the seasonal average was corrected using the mean deviation of three most recent observations from their expected seasonal values to generate forecasts for future months. The object was to capture trend in incidence during the most recent months while reducing statistical variation:

$$\hat{Y}_{t+m} = A_{t+m} + \frac{\sum_{i=0}^{2}(Y_{t-i} - A_{t-i})}{3}$$

The subscript $t - i$ denotes a month i lags before the (last) month t.

Autoregressive integrated moving average (ARIMA)
The autocorrelation pattern in each series at different time lags was used to develop ARIMA models (Box and Jenkins 1976). A single equation ARIMA model states how any value in a single time series is linearly related to its own past values through combining two processes: the autoregressive (AR) process

which expresses Y_t as a function of its past values, and the moving average (MA) process which expresses Y_t as a function of past values of the error term e:

$$Y_t = \phi_1 Y_{t-1} + \phi_2 Y_{t-2} + ... + \phi_p Y_{t-p} - e_t - \theta_1 e_{t-1} - \theta_2 e_{t-2} - ... - \theta_q e_{t-q}$$

where the ϕs and θs are the coefficients of the AR and MA processes, respectively, and p and q are the number of past values of Y_t and the error term used, respectively.

Application of the ARIMA technique requires the series to be stationary (i.e. with constant mean and variance over time). A series with constant variance can be obtained by applying log and other types of transformation to the original series. A constant mean can be obtained by taking the first or higher order difference of the variable as necessary until the series becomes stationary.

Seasonal and lag-1 differencing of the RI series (which were already on a log-scale) resulted in stationary series. The Akaike Information Criterion was used to compare goodness-of-fit among ARIMA models.

Assessment of forecast accuracy

The last 12 observations in each area were used for validation of forecast accuracy of the different methods and are referred to as test observations. For each area and each method, we generated 12 predictions at prediction intervals of 1,2,…,12 months for each of the 12 test observations. All predictions were made by using historical series of equal lengths, formed as subsets taken from the same series. For each prediction interval, average forecast error was then calculated. For example, in each area, the average 1-month ahead forecast error was calculated from all the 1-month ahead forecast errors produced for each of the 12 test observations. The average forecast error at prediction interval of m months (ε_m) was calculated as:

$$\varepsilon_m = \sqrt{\frac{\sum_{k=1}^{12} (Y_{t+m,k} - \hat{Y}_{t+m,k})^2}{12}}$$

where $Y_{t+m,k}$ and $\hat{Y}_{t+m,k}$ denote the observed and forecast values for month $t+m$ in sample k. The above error was again averaged over 20 areas (by

taking the arithmetic mean) to obtain the overall average error ($\bar{\varepsilon}_m$) of each method to forecast *m* months ahead.

We used observation periods of 30-48 consecutive months (depending on the data available) to generate forecasts for comparing accuracy among the different methods. We also tested forecast accuracy of the different methods by varying the observation period from 1 to 4 years. This was only possible for 7 data sets with sufficient length.

3.4 Results

Malaria transmission in most areas was highly variable from season-to-season and year-to-year. As an example, data from Finote Selam area (the longest series) shows a clear seasonal and inter-annual variation in incidence (Figure 3.1).

As was to be expected, forecast accuracy deteriorated as the prediction interval increased in the 20 study areas (Figure 3.2). This phenomenon, however, varied between methods: the most rapid deterioration of forecast accuracy with increasing prediction interval was observed for ARIMA, the slowest for the seasonal average method. The method using seasonal adjustment with mean deviation of last three observations almost consistently produced the lowest forecast error. This was true for most of the series (not shown). Up to about 9 months prediction interval, the average forecast error of this method was 0.22, i.e. 22% of the log mean number of cases in each area (95% CI: 0.17–0.27). The statistical sophistication of the ARIMA method did not result in better forecasts compared with the simpler methods. In most cases, the structures of the ARIMA models optimized for each series had similar structures, mainly consisting of both a non-seasonal and seasonal moving average or autoregressive parameters.

The effect of using different series lengths in forecasting was assessed using the seven longest series, by varying the lengths between 1 and 4 years. The overall average performed particularly well for a short historical series (1 year) and prediction intervals of up to 4 months (Figure 3.3a). This is partly a statistical phenomenon (only seven series were used) as forecast accuracy of the overall average method using 1-year data from all the 20 areas did not perform better than the seasonal adjustment method. Nevertheless, the shortest period of 1 year performed best for the overall average method, compared with longer periods. With the method using seasonal adjustment with last three observations, the average forecast error was minimal when lengths of 3 years were used (Figure 3.3b). This was also true for the other seasonal adjustment methods (not shown).

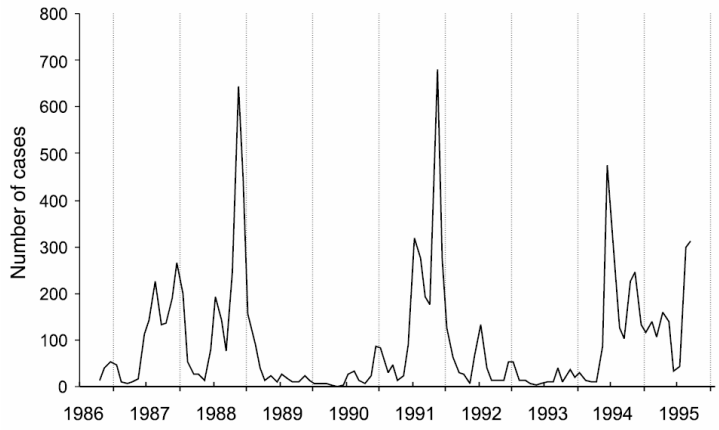

Figure 3.1 Incidence of *falciparum* malaria reported from Finote Selam Sector during the period September 1986–August 1995, showing seasonal and year-to-year variability of transmission.

Figure 3.4 shows comparison of predicted and observed values in actual number of cases for 1- and 12-month ahead forecasts for all areas using the overall best method: seasonal adjustment with last three observations. Overall, 1-month forecasts were better than 12-month forecasts (correlation coefficients between observed and predicted values were 0.50 and 0.45 at 1- and 12-month prediction intervals, respectively). It appears that incidence is less predictable during the dry season than during the wet season. The most predictable months in terms of incidence were the wet months of June–August as indicated by correlation coefficients between observed and predicted values ($r = 0.66$ and 0.75 at 1- and 12-month prediction intervals, respectively). The correlation coefficient during the usual malaria months of September–November was 0.55 at 1-month prediction interval. The most unpredictable months (at 1-month prediction interval) were the normally dry months of December–February ($r = 0.49$). At 12-month prediction interval, the periods September–November and December–February were most unpredictable ($r = 0.28$ and 0.31, respectively).

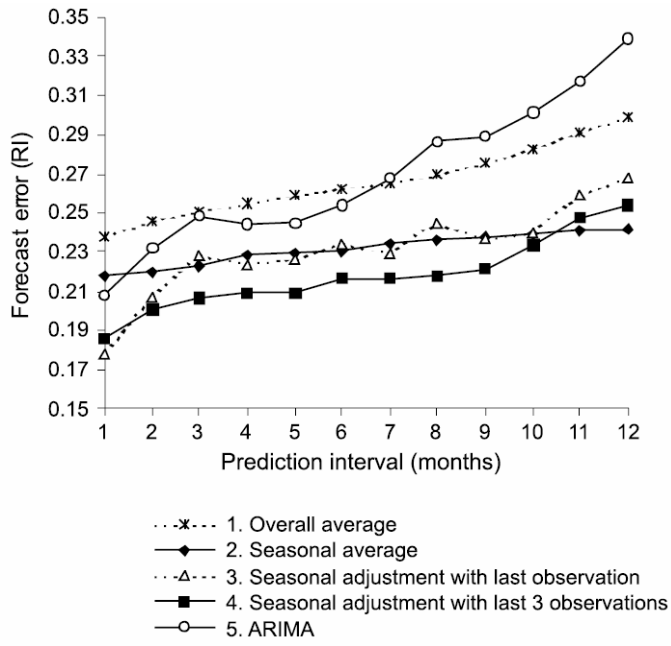

Figure 3.2 Accuracy of different forecasting methods calculated as average error of forecasts using 20 historical morbidity series. 30–48 months of observations were used to generate forecasts for each of the 20 areas. The errors are given on the relative (log) incidence (RI) scale. The methods are numbered in order of complexity.

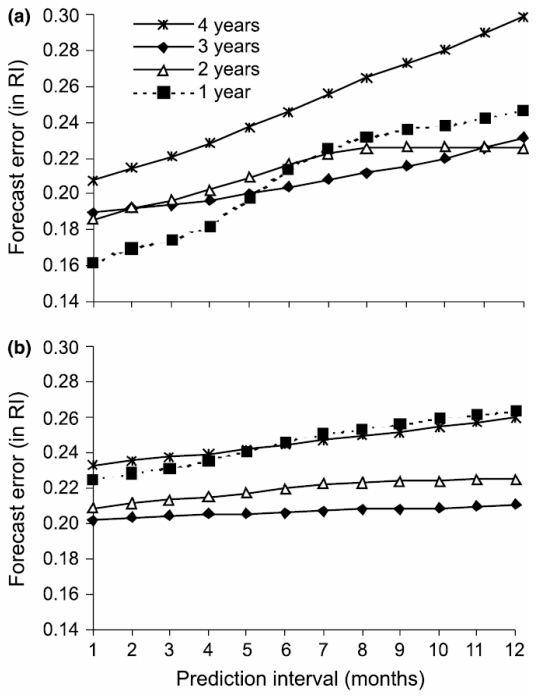

Figure 3.3 The effect of varying series length on forecast accuracy, for two of the methods: (a) overall average and (b) seasonal adjustment with last three observations (only areas with at least 6 years of observations were used; these include: areas 1, 2, 9, 10, 16, 18 and 19 as given in Table 3.1).

A practical method of calculating forecasts using the seasonal adjustment with last three observations in a malaria epidemic early warning system (in the absence of a better method) is suggested in the Appendix.

3.5 Discussion

In this study, different methods were compared with forecast of malaria incidence from historical morbidity patterns in areas with unstable transmission to assess their potential use in epidemic early warning. The potential use of time series techniques, especially the ARIMA method, in epidemiological studies, disease surveillance and outbreak forecast, has been explored in some studies (Helfenstein 1991; Allard 1998). In our study, methods using seasonal adjustment were found to produce relatively better forecast of malaria incidence compared with the ARIMA method. Other studies have also indicated that the statistically advanced ARIMA models may produce very good fit to the data but in post-sample forecast, they would not be robust enough to handle a possible change in behaviour of the series (Makridakis *et al.* 1998).

Seasonal adjustment which takes account of deviations from seasonal averages of the last three observations gave the best forecast compared with the other methods. This is because of the capability of the method to accommodate both seasonality and recent changes or trends at the same time. However, this method gave only about 20% improvement relative to the overall average and about 10% compared with the seasonal average method.

There is always a balance between statistical accuracy and time trends. Very long series lead to relatively accurate averages, but they capture trends poorly. In contrast, very short series capture recent trends very well, but the averages they produce are relatively less accurate compared with those from longer series. All the methods used in this study differ in their sensitivity to length of the series used to generate forecasts. For example, the seasonal adjustment with last three observations performed best when 3 years' observations were used. On the other hand, the overall average method performed best with 1-year data. The results indicate the need for balancing short historical series (i.e. data closer to the prediction period) with long-enough series to minimize random error.

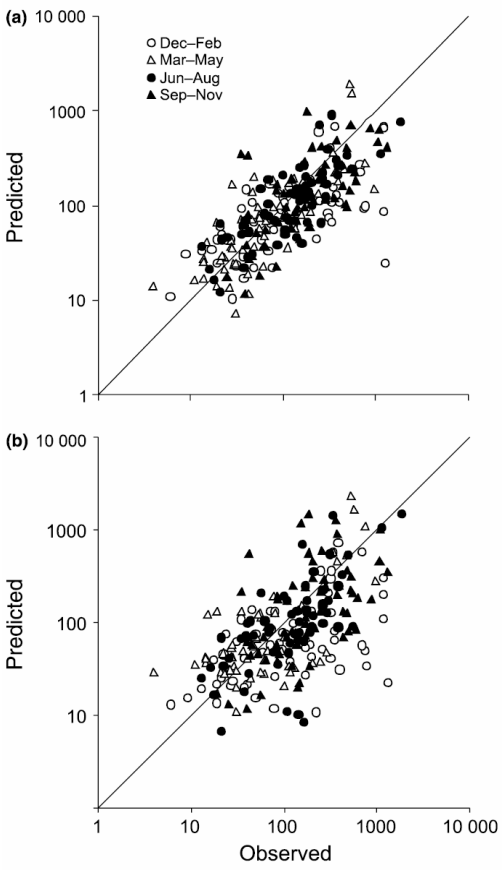

Figure 3.4 Comparison of observed and predicted number of cases in the 20 study areas using seasonal adjustment with the last three observations. (a) One-month prediction interval and (b) 12-month prediction interval.

There is little doubt that external forces contribute significantly to variations in incidence levels. Several studies have shown that severe malaria epidemics are associated with changes in meteorological variables such as those resulting from EL Niño events (Bouma *et al.* 1996; Lindsay and Birley 1996; Bouma and Dye 1997; Kilian *et al.* 1999). On the other hand, the fact that consistently better forecasts were obtained for shorter term forecasts indicates that there is also some contribution of the inherent pattern in the historical morbidity data that may be considered in multivariate models. In a time series analysis conducted in Kenya, Hay *et al.* (2001) have shown that in an area with unstable transmission, climate variables might have a significant contribution to malaria epidemics, but in areas with higher endemicity, there is a between-year signal that is not related to climate, and rather may be the result of basic dynamics of the disease. The authors therefore suggest that in such cases, systems for epidemic early warning that ignore parasite and host population dynamics are unlikely to be sufficiently robust to capture super-annual variation in disease risk.

Figure 3.4 illustrates the goodness-of-fit of 1-month ahead forecasts compared with those of 12 months ahead, using the overall best seasonal adjustment method. As is clear from Figures 3.2 and 3.3b, 1-month ahead forecasts are much better than longer prediction intervals. Nevertheless, in terms of epidemic early warning, the accuracy of forecasts is still not acceptable. For example, predictions for 100 observed cases may range approximately from 20 to 500 cases.

The results of the present analysis show that simple methods such as seasonal adjustments perform as well as or even better than the more advanced ARIMA method, although they are themselves not accurate enough for forecasting abnormal incidence for use in an epidemic early warning system, especially during the dry season. The size of the forecast errors should also be cautiously interpreted as a result of gross underestimation of the true number of cases by health service data, especially during epidemics. An abnormal increase of malaria leads to excess cases visiting health facilities beyond their maximum capacity. Severe epidemics usually occur in remote rural areas far away from health facilities, and during such periods, health workers have to travel to those areas to distribute antimalarial drugs. Such house-to-house treatment of cases is normally not part of the reported morbidity data. In areas with highly unstable transmission, the use of external predictor variables (e.g. temperature and rainfall) together with past pattern of incidence, would probably lead to more accurate predictions of epidemics. Development of such models is under investigation.

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Appendix

We present below a practical suggestion for using the seasonal adjustment method which performed best in our study for forecasting malaria incidence using historical morbidity patterns. This procedure may be used (or adapted to local situations) by malaria control programmes in their epidemic early warning systems in the absence of better methods of forecasting epidemics.

To generate forecasts, use the last 36 monthly malaria morbidity data (e.g. clinically diagnosed malaria cases, microscopically confirmed *P. falciparum* cases) diagnosed at a health facility or groups of health facilities in a specific area, which may be a selected sentinel surveillance site (based on our study, series longer than 3 years may not account for time effects. Shorter series are not accurate enough to provide seasonal averages).

Enter the data in a spreadsheet programme. In a new column, calculate the natural logarithms of each monthly observation.

In a separate column, for each calendar month, calculate the 'expected' seasonal average from the log-transformed series. For example, for the month of July, the mean from the three log-transformed observations during the three previous years will be the expected seasonal average for July.

Now you have all the necessary information to forecast incidence in the future. If the last month for which you have observations is July, and you need to generate forecasts for the next 2 months (August and September), proceed as follows:

Starting from July backwards, calculate the difference between each of the last three observations and their respective seasonal averages.

Take the mean of the three differences (or deviations).

To generate a forecast (on a log-scale) for August, add the mean deviation obtained above to the expected seasonal average for August. To generate a forecast for September, add the same mean deviation obtained above to the expected seasonal average for September.

Now you have forecasts on a log-scale, you need to back-transform your forecasts to the normal scale (i.e. number of cases). To do this, take the exponent of each of the (log-scale) forecasts. Finally, the obtained forecasts should always be interpreted with caution, as high degree of accuracy cannot be guaranteed.

4

Spatial and temporal variations of malaria epidemic risk in Ethiopia: factors involved and implications

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4.1 Summary

The aim of this study was to describe spatial and temporal variations in malaria epidemic risk in Ethiopia and to examine factors involved in relation to their implications for early warning and interpretation of geographical risk models. Forty-eight epidemic episodes were identified in various areas between September 1986 and August 1993 and factors that might have led to the events investigated using health facility records and weather data. The study showed that epidemics in specific years were associated with specific geographical areas. A major epidemic in 1988 affected the highlands whereas epidemics in 1991 and 1992 affected highland-fringe areas on the escarpments of the Rift Valley and in southern and north-western parts of the country. Malaria epidemics were significantly more often preceded by a month of abnormally high minimum temperature in the preceding 3 months than based on random chance, whereas frequency of abnormally low minimum temperature prior to epidemics was significantly lower than expected. Abnormal increases of maximum temperature and rainfall had no positive association with the epidemics. A period of low incidence during previous transmission seasons might have aggravated the events, possibly due to low level of immunity in affected populations. Epidemic risk is a dynamic phenomenon with changing geographic pattern based on temporal variations in determinant factors including weather and other eco-epidemiological characteristics of areas at risk. Epidemic early warning systems should take account of non-uniform effects of these factors by space and time and thus temporal dimensions need to be considered in spatial models of epidemic risks.

4.2 Introduction

Malaria mostly affects children in highly endemic areas with stable transmission. In areas with low or moderate endemicity, all age groups are affected and such areas are at a special risk of severe epidemics. Epidemic malaria has been defined as a periodic sharp increase in incidence that is clearly in excess of the usual, although the application of such a definition to actual situations is not always straightforward (MacDonald 1957; Molineaux 1988).

Ethiopia is among the most affected countries by malaria epidemics, mainly due to its varying topographical and climatic features. The western, central and eastern highlands and highland-fringe areas along the Rift Valley are especially prone to periodic malaria epidemics. (Craig *et al.* 1999) have shown that large areas in the western and central Ethiopian highlands are unsuitable for malaria transmission in the average year, and a climate-based spatial model of epidemic risk of various areas of the country has been proposed (Cox *et al.* 1999).

In most parts of Ethiopia, a short transmission season followed by a long interval of very low or no transmission results in little effective immunity acquired by the population. Distinct from the ‘‘normal’’ seasonal increase in many areas, major periodic epidemics have occurred in the country from time-to-time. In 1958, an epidemic resulted in an estimated three million cases out of which 150,000 people died (Fontaine *et al.* 1961). Similar epidemics affected the country at varying intervals.

In this study we describe the spatial and temporal variations in malaria epidemic risk in Ethiopia using retrospective morbidity and ground meteorological data and variations in possible precipitating factors in relation to their implications for future development of epidemic early warning systems and interpretation of geographically-oriented risk models.

4.3 Materials and methods

Data

Malaria morbidity data reported from Sector Malaria Control Offices (SMCOs) between September 1986 and August 1993 were used in the analysis (A sector is an area delineated for purpose of malaria control and covered approximately two to five districts, each with approximately 75,000-

150,000 inhabitants). Data after August 1993 was not used due to changes in the organizational structure of the malaria control programme. The morbidity data comprised microscopically confirmed cases seen at Malaria Detection and Treatment Posts (MDTPs) located in catchment areas of SMCOs.

A total of 50 sectors (out of 59) for which data was available for at least 50 months were included in the analysis. All confirmed *Plasmodium falciparum*, *P. vivax*, *P. malariae* or mixed infections with fever were defined as malaria cases and used in the study. For most of the sectors, compiled data was not available for the period September 1989-August 1990. On average data was available for 63 months out of the total 84 months. We assumed that among the confirmed cases reported by MDTPs monthly, the majority were diagnosed at malaria laboratories based at the SMCOs. Furthermore, in view of limited modes of transportation in rural areas, it is very likely that most of the malaria cases seen at a sector's malaria laboratory originated from localities not far away from the base towns of the sectors.

Data relating to rainfall, minimum and maximum temperatures of the base town of sector offices were obtained from the National Meteorological Services Agency of Ethiopia. Among the 50 sectors, 35 had meteorological data for detailed analysis concerning weather anomalies in relation to abnormal incidence.

Statistical methods

Abnormal incidence

The monthly morbidity data have a lognormal distribution, and therefore analysis was based on log-transformed series. In about 3% of the observations where all examined patients were negative for malaria throughout the month, 1 case was assumed instead of 0. For each sector and each calendar month, the historical average and standard deviation were calculated. Departure of the observed number of cases from the expected (geometric mean) for each sector and calendar month was standardised by dividing it by the corresponding standard deviation calculated separately for each sector and month. The resulting index represents the number of standard deviations by which observed number of cases departs from the expected and varies approximately between +2 and -2. An epidemic period was defined if observed log number of cases exceeded the expected plus one standard deviation for at least 3 consecutive months. Similarly, a period of abnormally low incidence was defined if observed log number of cases was below the expected minus one standard deviation for at least 3 consecutive months. Sectors were subsequently grouped by year of epidemic onset. For sectors with double

epidemic episodes, the most intensive was used for group classification. Intensity was determined by the total ''excess'' departure beyond the (expected) mean plus one standard deviation limit. The groups were then described in terms of topography, geographic location, and climate, and the trend of the standardised departure index was explored over the study period.

To study the association of epidemics with a period of abnormally low incidence during previous transmission seasons in relation to immunity status of affected populations (as a function of intensity of past transmission), we compared the normality of incidence 1 and 2 years before each epidemic onset. The previous years' period used for comparison included the onset month with 1 month before and after it. Data was available for 37 episodes during the previous year and for 30 episodes for the period 2 years earlier.

Weather anomaly

The trend of abnormal weather conditions (weather anomaly) was studied using a similar departure index used for studying abnormal incidence. For each sector and each calendar month, the ''expected'' mean and standard deviation of minimum and maximum temperature and rainfall were calculated from monthly weather records between June 1986 and August 1993. The mean and standard deviation of rainfall was calculated after cubic root transformation of the monthly records to obtain Normal distribution. For each month, an abnormal weather condition was defined for each variable if observed values were below -1 or above 1 standard deviation from the mean.

In 35 sectors with weather data, the frequencies of abnormal meteorological variables were calculated for the period up to 3 months before the onset of each epidemic episode and each period of abnormally low incidence. These frequencies were then compared to expected frequencies of values beyond -1 or 1 from the Normal distribution during the 3-month periods. In case of a perfect Normal distribution, 15.9% of observations will exceed 1 standard deviation and the same percentage will be below -1 standard deviation. This means that for periods of 3 months, we can expect 40.5% to contain at least 1 month of abnormal weather: $1-(1-0.159)^3 = 0.405$. The expected value can be somewhat different if the distribution is deviating from normal. By means of Chi-square testing with 1 degree of freedom, we tested whether observed presence of abnormal weather in the 3 months preceding onset of an epidemic or a period of abnormally low incidence differed from expected.

4.4 Results

Plasmodium falciparum infections constituted 68% of the total 920,836 cases reported from 50 sectors; most of the remaining were *P. vivax* infections. *P. falciparum* showed a higher degree of seasonal variation compared to *P. vivax* (Figure 4.1). On average, the peak malaria month was October, following a smaller peak in July. In 88% of the 50 sectors, maximum incidence occurred between June and November.

An example of the procedure used to identify periods of abnormal incidence is shown in Figure 4.2 with plots of the monthly observed and expected numbers of cases with the upper and lower limits of the mean plus/minus one standard deviation for one of the sectors—Asela. In this sector, July 1988-January 1989 was identified as an epidemic period.

Forty-eight epidemic episodes were identified in various areas between September 1986 and August 1993. Half of these episodes were due to abnormal increases of both *P. falciparum* and *P. vivax* cases; 13 episodes were due to abnormal increase of *P. falciparum* and 11 due to *P. vivax*. Thus, 77% of the epidemic episodes involved *P. falciparum*.

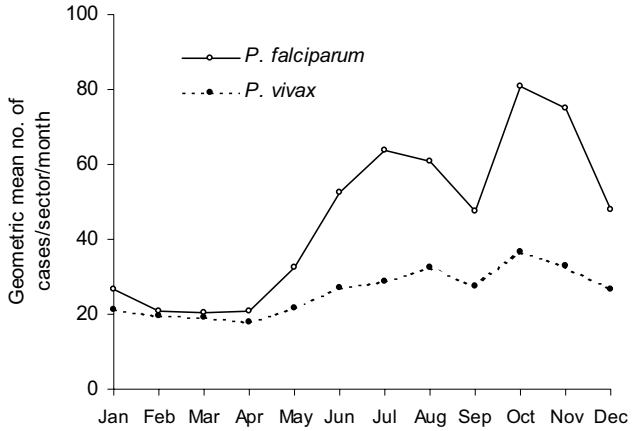

Figure 4.1 Seasonal variations in incidence of *P. falciparum* and *P. vivax* malaria in Ethiopia (September 1986 - August 1993).

The study showed that epidemic episodes in specific years were associated with different areas that had specific geographic characteristics. In 23 sectors (46%), incidence was abnormally low during the usual malaria season of 1986, but gradually increased from the second half of 1987 onwards. An unusual increase affected several sectors across the country, later to develop to a major epidemic covering a wide geographical area (4 sectors in 1987, 21 sectors in 1988) (Table 4.1). In 1991 and 1992, other epidemics affected 14 other sectors. Double epidemic episodes were observed in nine of the sectors. According to the criteria used, incidence was considered ''normal'' in 10 sectors during the period under study.

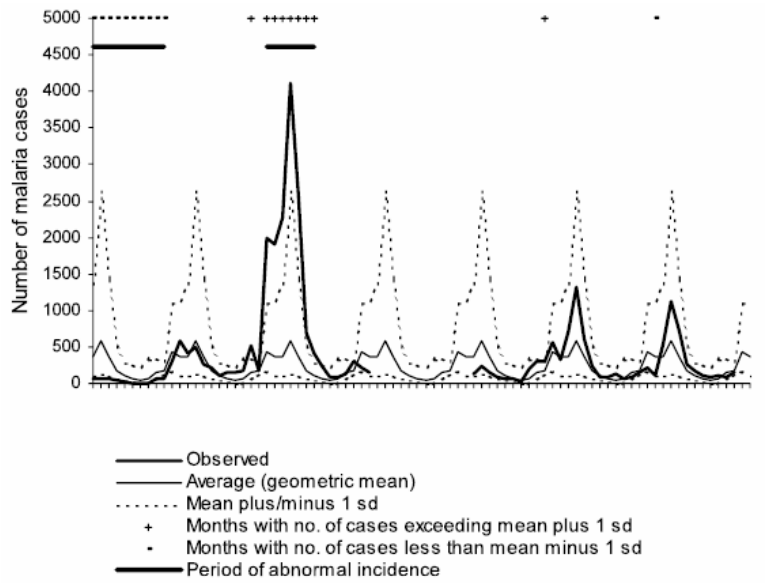

Figure 4.2 Observed and expected number of malaria cases in Asela Sector. Data analysis was based on log-transformed observations; results are shown after back-transformation. No observations are available from September 1989 to August 1990.

The 1987 epidemic affected few areas in the western lowlands. The 1988 epidemic was the most widespread, affecting the western and central highlands (Figure 4.3). Nearly three-quarters of the sectors affected in 1988 were highlands classified under warm-temperate rainy climate (Gonfa 1996), with low annual mean temperature and high annual rainfall, with mean altitude of the base towns of nearly 2000 m (Table 4.2).

On the other hand, the 1991 and 1992 epidemics affected the north-eastern and eastern areas on both escarpments of the Rift Valley, areas in the vicinity of Lake Tana, some areas bordering the eastern and southern lowlands, and central and southern highland-fringe areas in the narrow portion of the Rift Valley (Figure 4.3). The base towns of sectors affected in 1991 or 1992 were at significantly lower altitude compared to those affected in 1988 ($P = 0.006$).

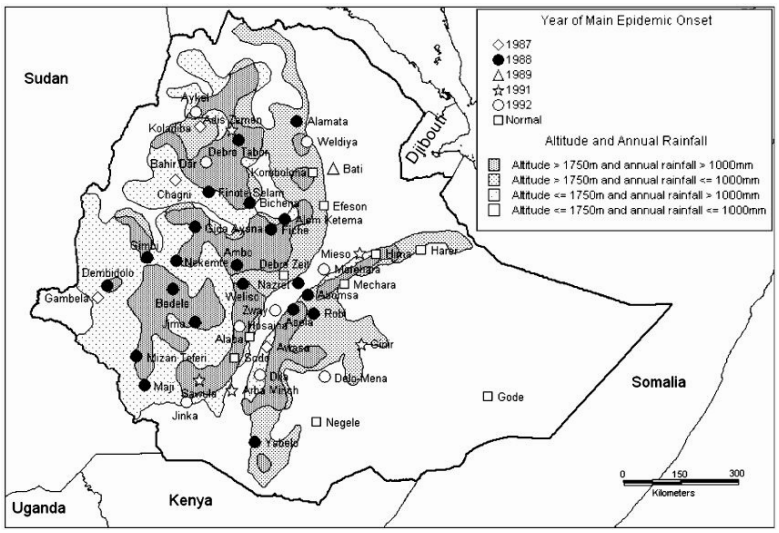

Figure 4.3 Geographic and climatic distribution of sectors grouped according to year of onset of malaria epidemics during September 1986-August 1993. Map contours were adapted from (Gonfa 1996) and National Meteorological Services Agency of Ethiopia (1989).

Sectors with incidence considered 'normal' during the period under study were located in areas bordering the dry north-eastern and the south-western sections of the Rift Valley, and the eastern arid lowlands (Figure 4.3). These areas are characterised by significantly less annual rainfall compared to those affected in 1988 ($P = 0.01$), and 1991-92 ($P = 0.09$).

Meteorological data was available for 35 sectors out of the total 50. Among the 1988 group 15 sectors and among the 1991-92 groups 9 sectors had weather data. Average anomalies of incidence and weather variables were calculated for these groups separately (Figure 4.4a-d). In both areas affected in 1988 and 1991-92, anomaly of malaria incidence gradually increased from very low levels in late 1986 to a peak in 1988, after which it declined sharply in 1989 to below normal levels (Figure 4.4a). In areas affected in 1991-92, incidence anomaly was still negative during late 1987 whereas it was already above normal in areas affected by the 1988 epidemic.

Thirty of 37 episodes for which morbidity data was available a year before were preceded by normal incidence and 7 by a period of abnormally low incidence during the previous year. Furthermore, 18 of a total 30 epidemic episodes were preceded by normal incidence and 12 by a period of abnormally low incidence 2 years earlier. This was particularly evident prior to the 1988 epidemic (Figure 4.4a). Similarly, although morbidity data was not available for most areas during the period September 1989-August 1990, reports from one sector (Finote Selam) indicated that incidence was much below normal during the period prior to the 1991 epidemic (not shown).

During most of 1987 and 1988, minimum temperature was above normal in all areas (Figure 4.4b). In the sectors affected in 1988, minimum temperature anomaly was slightly higher than those affected in 1991-92 during the peak months of the epidemic. The trend of minimum temperature anomaly before the 1988 epidemic followed different patterns in areas affected in 1991-92 compared to the 1988 group. A delay of several months was observed before anomaly started increasing in the 1991-92 group. Towards the end of 1988, this anomaly quickly came to normal and continued to drop further to abnormally low levels in a similar manner as incidence anomaly. From about mid 1989, minimum temperature anomaly started to rise again in all areas, and so did incidence anomaly. From 1991 onwards, minimum temperature anomaly was higher in the 1991-92 epidemic areas compared to the 1988 epidemic areas. Maximum temperature and rainfall anomalies followed similar trends in both the 1988 and 1991-92 groups (Figure 4.4c-d).

Table 4.1 Grouping of sectors in Ethiopia based on onset of epidemic episodes during September 1986-August 1993

Group	Time of epidemic onset (quarter and year)	No. of sectors	List of sectors
1987	II-87	1	Chagni
(4 sectors)	IV-87	3	Koladiba, Gambela, Awasa
1988	II-88	5	DebreTabor, Fiche,
(21 sectors)			Ambo, Jima, Yabelo
	III-88	8	Finote Selam, Gida Ayana, Nekemte, Dembidolo, Bedele, Bichena, Nazret, Asela
	IV-88	5	Alamata, Alem Ketema, Maji, Weliso, Robi
	II-88, IV-88	1	Abomsa
	III-88, II-91	1	Mizan Teferi
	III-88, I-93	1	Gimbi
1989	II-89, II-91	1	Bati
(1 sector)			
1991	III-91	2	Adis Zemen, Ginir
(5 sectors)	IV-91	2	Mieso, Sawula
	I-91, IV-92	1	Arba Minch
1992	I-92	1	Metehara
(9 sectors)	I-92, III-91	1	Delo-Mena
	III-92	3	Zway, Dila, Jinka
	IV-92	1	Hosaina
	IV-92, III-91	2	Bahir Dar, Weldiya
	IV-92, I-87	1	Aykel
Normal during Sep 86-Aug 93 (10 sectors)	—	10	Kombolcha, Efeson, Debre Zeit, Hirna, Harer, Alaba, Sodo, Mechara, Negele, Gode

In the case of more than one episode, the most intensive was used to group sectors.

Epidemics were significantly more often preceded by a month of abnormally high minimum temperature in the preceding 3 months than based on random chance (Figure 4.5). The frequency of abnormally high minimum temperature during a 3-month period prior to 27 epidemic episodes was 51.9% compared to the expected 35.9% ($\chi_1^2 = 3.02; P = 0.082$), whereas the same frequency prior to abnormally low incidence was only 21.2% ($\chi_1^2 = 3.06; P = 0.080$). The frequency of abnormally low minimum temperature preceding epidemics was significantly lower than expected ($\chi_1^2 = 4.52; P = 0.033$). The results indicate that abnormally low and high minimum temperatures are associated with epidemics in a reverse way. On the other hand, abnormally increased maximum temperature and rainfall had no positive association with epidemics as their frequencies were below expected values of 42.2% and 41.0%, respectively.

Table 4.2 Characteristics of sectors affected by malaria epidemics in 1987, 1988 and 1991-92 in comparison with unaffected sectors.

Characteristics	Year of main epidemic	Mean (sd)	*n*	Std. error of mean
Altitude (m)	1987	1394 (612)	4	305.9
	1988	1996 (359)	21	78.4
	1991-92 [a]	1644 (325)	15	84.0
	Not affected	1701 (534)	10	169.0
Mean temperature (°C)	1987	22.2 (4.3)	3	2.51
	1988	18.6 (2.4)	19	0.54
	1991-92	20.3 (2.3)	14	0.62
	Not affected	20.2 (3.4)	8	1.21
Mean annual rainfall (mm)	1987	1220 (341)	4	170.3
	1988	1310 (442)	20	98.8
	1991-92	1120 (348)	14	93.1
	Not affected	887 (289)	9	96.2

[a] Includes Bati Sector which was affected both in 1989 and 1991.

4.5 Discussion

The study showed that different epidemics in specific years were associated with different areas that had specific geographic characteristics. The 1988 epidemic affected the normally cool and rainy highlands, whereas most of the low-lying areas in southern and eastern parts of the country remained unaffected. On the other hand, epidemics in 1991 and 1992 affected highland-fringe areas on the escarpments of the Rift Valley and in the southern and north-western parts of the country. Nearly all the epidemic areas in 1988 were not affected in 1991 or 1992, and conversely those affected in 1991 or 1992 were free of epidemics in 1988, indicating a changing risk pattern over time.

Although a detailed exploration of the statistical associations between possible precipitating factors and epidemics is not the subject of the present paper, the study indicates that aberrant conditions in weather phenomena, in particular abnormal increase in minimum temperature, might have led to abnormal increases in incidence coupled with lack of immunity in affected populations probably resulting from low levels of incidence in pre-epidemic periods. We have previously demonstrated that incidence in areas with unstable transmission may not be predicted well from historical morbidity patterns alone (Abeku *et al.* 2002). In the highland areas at risk, monitoring minimum temperature as well as recent trends in incidence could provide a basis for epidemic early warning. Detailed quantitative analysis of the effect of meteorological and other precipitating factors as determinants of epidemics is necessary in developing prediction models and this work is currently underway. Highland areas above 2000 m altitude have been frequently referred to as 'non-malarious' in Ethiopia; although at times they have been affected by more severe epidemics resulting in higher mortality compared to moderately malarious areas. The presence of the Rift Valley across Ethiopia is a significant factor in the epidemiology of malaria in the country. Seasonal transmission is sustained from year to year in the warm lowlands of the valley. In these areas, seasonality is mainly a function of rainfall alone and/or temperature. In the presence of reservoirs of infection in the Rift Valley, the surrounding highlands and highland-fringe areas can be affected by severe epidemics when weather conditions, especially temperature, become favourable for transmission in populations with low immunity. Schaller and Kuls (Schaller and Kuls 1972) have reported that epidemic-prone hypoendemic zones of malaria occurrence are mainly at altitudes between 1600 and 2000 m. The 1958 epidemic also affected highlands between 1600 and 2150 m elevation (Fontaine *et al.* 1961). A climate-based model of malaria distribution has indicated that large areas in the western and central Ethiopian highlands are unsuitable for malaria transmission in the average

year. An extensive review of the history of malaria epidemics in Ethiopia and a climate-based spatial model of epidemic risk of various areas of the country has been presented by (Cox *et al.* 1999). These maps give important insights regarding the magnitude of epidemic risks in different areas, but their use and interpretation should take into account the temporal variation of the geographic risk pattern as described in the present study.

Factors such as increased drug resistance by *P. falciparum*, insecticide resistance by vectors, civil war, population migration, and changes in the quality and coverage of health service interventions might have contributed to the severity of the observed epidemics. Drug or insecticide resistance usually cause gradual increases in incidence over several years. The levels of drug resistance by *P. falciparum* and DDT resistance by the major vector *Anopheles arabiensis* were low in the 1980s in Ethiopia (Teklehaimanot 1986; Abose *et al.* 1998), although in the 1990s resistance to chloroquine increased, probably contributing to later epidemics. It has been also reported that high population migration towards the end of the civil war in relation to spreading chloroquine-resistant *falciparum* malaria might have played a role in the localised epidemics of 1991 (Mengesha *et al.* 1998).

Changes in weather conditions probably played major roles as the cause of most of the severe epidemic episodes in Ethiopia. The present study shows that any abnormal increase in minimum temperature is very likely to lead to malaria epidemics in Ethiopian highlands. In the lowlands, rainfall might play a significant role in determining the risk of malaria epidemics. The main cause of the 1958 epidemic was suggested to be unusually high rainfall and abnormally high temperature and humidity which prevailed in the highlands (Fontaine *et al.* 1961). On the other hand, epidemics in years of deficient rainfall have been noted (Covell 1957). Epidemiological observations made in February—April 1994 in Sodo area, southern Ethiopia have shown that epidemics also affected the highlands as the result of an abnormally extended dry season (unpublished report, Ministry of Health, Ethiopia). During such events, vectors breed extensively in pools of intermittent rivers and streams, and heavy rainfall tends to interrupt transmission by destroying mosquito breeding sources. In Debre Zeit, central Ethiopia, the years and months with increased temperature and decreased rainfall were associated with El Niño events, which were in turn associated with increased malaria incidence (Tulu 1996).

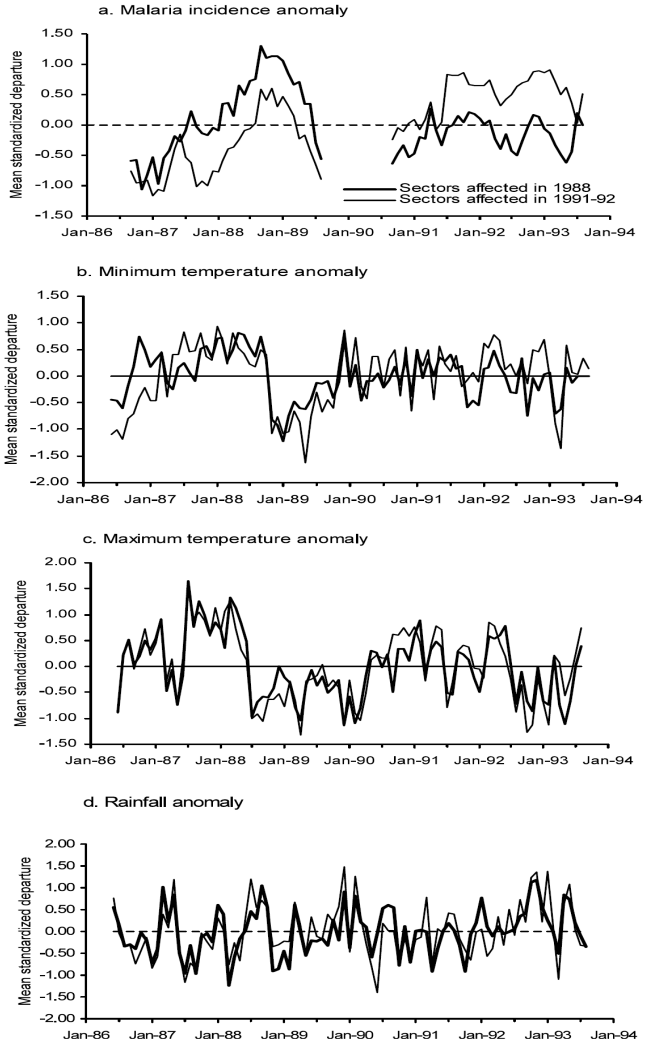

Figure 4.4 Anomalies of malaria incidence and meteorological variables in areas affected by epidemics in 1988 and 1991-92. (Weather data was available for 15 out of 21 sectors and 9 out of 15 sectors for the 1988 and 1991-92 groups, respectively).

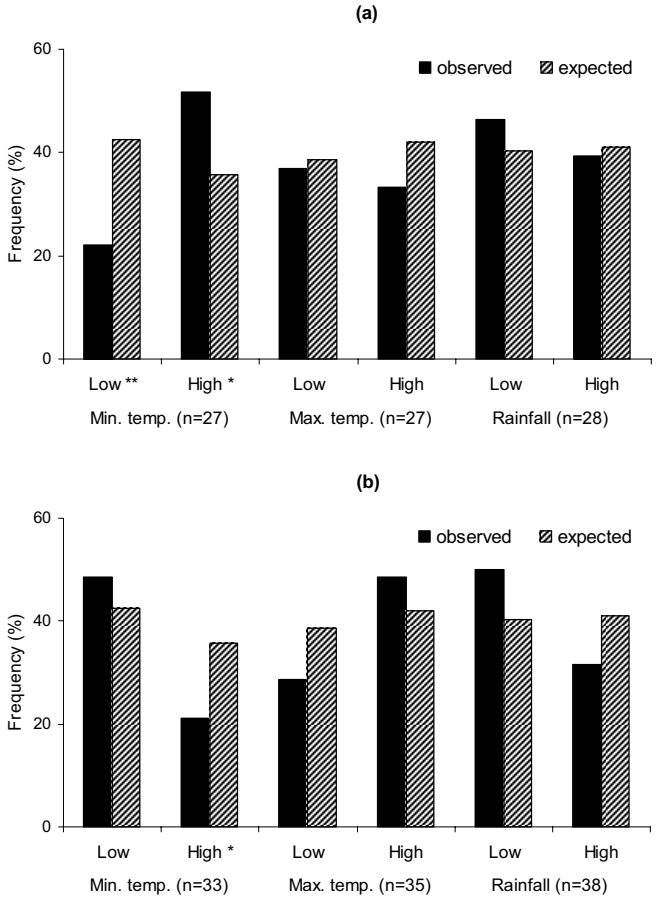

Figure 4.5 Observed and expected frequencies of abnormally high and abnormally low values of weather variables for at least 1 month during a 3 month period before: (a) epidemic episodes, and (b) abnormally low incidence. Significant differences at 5% and 10% significance levels between observed and expected values (Chi-square test) are indicated with the x-axis labels as ** and *, respectively. (Abbreviations: Min. temp. = minimum temperature; Max. temp. = maximum temperature).

This study showed that epidemics in specific years were associated with specific geographic patterns, indicating spatial as well as temporal variations of risk. Epidemic risk is a dynamic phenomenon with changing geographic pattern according to temporal variations in precipitating factors including the interplay of weather anomalies, topography and other eco-epidemiological features. Weather anomalies (especially increased minimum temperature) during the late 1980s and early 1990s might have caused the identified epidemics, but their impact showed high degree of variation between areas with differing epidemiological features. Low immunity status in the populations affected due to abnormally low incidence during transmission seasons prior to the epidemic events probably aggravated the effects of weather anomalies and resulted in high morbidity levels. The challenge to health services in Ethiopia is to develop a capacity for epidemic early warning that takes into account non-uniform effects of various precipitating factors by space and time.

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5

Effects of meteorological factors on epidemic malaria in Ethiopia: a statistical modelling approach based on theoretical reasoning

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5.1 Summary

This study was conducted to quantify the association between meteorological variables and incidence of *Plasmodium falciparum* in areas with unstable malaria transmission in Ethiopia. We used morbidity data pertaining to microscopically confirmed cases reported from 35 sites throughout Ethiopia over a period of approximately 6-7 years. A model was developed reflecting biological relationships between meteorological and morbidity variables. A model that includes rainfall 2 and 3 months earlier, and mean minimum temperature of the previous month and *P. falciparum* case incidence during the previous month was fitted to morbidity data from the various areas. The model produced similar percentages of over-estimation (19.7% of predictions exceeded twice the observed values) and under-estimation (18.6% were less than half the observed values). Inclusion of maximum temperature did not improve the model. The model performed better in areas with relatively high or low incidence (>85% of the total variance explained) than those with moderate incidence (55%-85% of the total variance explained). The study indicated that a dynamic immunity mechanism is needed in a prediction model. The potential usefulness and drawbacks of the modelling approach in studying the weather-malaria relationship are discussed, including a need for mechanisms that can adequately handle temporal variations in immunity to malaria.

5.2 Introduction

Epidemic malaria remains a major public health concern in highland and arid areas in tropical countries (Lindsay and Martens 1998; Nájera *et al.* 1998). Changes in weather conditions probably played a major role as the cause of most of the severe epidemics. Increased temperature in cooler environments shortens the parasite's life cycle within the vector, thus increasing transmission probability before the mosquito vector dies (MacDonald 1957; Molineaux 1988). Increased temperature would also increase the rate of mosquito emergence from breeding places, and in the presence of rainfall increased humidity results in longer survival of the vector to transmit the parasite (Hay *et al.* 2000). Rainfall also affects the abundance of mosquito breeding sites.

In the Ethiopian highlands, several large-scale epidemics have been reported since the 1950s. In 1958, an estimated 150,000 people died during a widespread epidemic of malaria in the highlands (Fontaine *et al.* 1961). Several epidemics have been reported since then. Abnormal transmission of unusual proportions has affected the highlands and highland-fringe areas in 1988 and 1991-92 which was associated with abnormally increased minimum temperature (Abeku *et al.* 2003). More recently, epidemics have occurred in the highlands during the second half of the last decade; in particular a widespread epidemic in 1998 was largely attributed to an El Niño event (unpublished data). The association of abnormal weather conditions and increased malaria incidence has been reported in several studies. In the Punjab province of India, epidemics were shown to be significantly more prevalent in a year with a wet (high) monsoon rainfall following a dry El Niño year than in other years, while in Sri Lanka, epidemics were significantly more prevalent during El Niño years, when the same south-west monsoon tends to fail (Bouma and van der Kaay 1996). In Venezuela, malaria significantly increased in the year following an El Niño event (Bouma and Dye 1997).

Currently there is a need for systems for epidemic early warning in areas at risk (Myers *et al.* 2000; Thomson and Connor 2001). Previously, we have demonstrated that incidence in areas with unstable transmission may not be predicted well from historical morbidity patterns alone even when a statistically more sophisticated ARIMA (autoregressive and integrated moving average) method is used (Abeku *et al.* 2002). In areas with highly variable transmission, the use of predictor variables such as temperature and rainfall together with past patterns of incidence might lead to more accurate predictions.

The aim of this study was to quantify the effects of meteorological factors on malaria incidence in areas with unstable transmission using a statistical model based on theoretical reasoning. On the basis of biological arguments, we derived a linear mixed model for monthly data including rainfall, temperature and incidence of confirmed *Plasmodium falciparum* cases reported from 35 sites across Ethiopia. We also tested whether extending the model by including more variables would significantly improve the basic model. Moreover, we compared the performance of the basic model with methods that use historical morbidity patterns for studying the impact of weather variables on incidence after one month interval.

5.3 Materials and methods

Data used for analysis

We used malaria morbidity data (microscopically confirmed cases) reported from 35 Sector Malaria Control Offices (SMCOs) throughout Ethiopia between September 1986 and August 1993. A sector is an area delineated for the purpose of malaria control and covers 2-5 districts, each with approximately 75,000 to 150,000 inhabitants. The malaria cases were seen at Malaria Detection and Treatment Posts (MDTPs) located in catchment areas of SMCOs, which are supposed to report to their respective SMCOs every month. We assumed that among the confirmed cases reported monthly, the majority were diagnosed at malaria laboratories which were based at the SMCOs. Most of the other MDTPs (e.g. health centres, hospitals, etc.) irregularly report to SMCOs and when they do, the reports constitute only a small proportion of the total confirmed cases in each sector. Furthermore, in view of the limited modes of transportation in rural areas, it is very likely that most of the malaria cases seen at a sector's malaria laboratory originated from localities not far away from the base town of the sector.

During September 1986–August 1993, on average 320 confirmed malaria cases were reported per sector per month. *P. falciparum* and *P. vivax* constituted 68.7% and 31.3% of the total 604,589 malaria-positive cases, respectively. To study the seasonal pattern of malaria at different altitudes, the sectors were grouped as 'highlands' (above 1750 m, n = 18) and 'lowlands' (1750 m and below, n = 17). Both groups have a similar seasonal pattern of incidence (Figure 5.1a) with a peak in *P. falciparum* incidence in October (*P. vivax* showed much less inter-seasonal variation). The high degree of seasonality of *falciparum* malaria is closely associated with seasonal variation in rainfall and temperature. Weather data between January 1950 and

December 1998 (monthly rainfall, and minimum and maximum temperatures) and altitudes of base towns of the SMCOs were obtained from the National Meteorological Services Agency of Ethiopia (Table 5.1). In most areas, the main rainy season is between June and September with peak rains falling in July and August (Figure 5.1b). On average, the highland sectors received more rainfall than did the lowlands. Average daily temperature in the highlands ranged from 17.1 ^{o}C in December to 19.5 ^{o}C in April, whereas in the lowlands, it ranged from 20.7 ^{o}C in December to 30.6 ^{o}C in March. Mean monthly minimum and maximum temperatures differed (as expected) between highlands and lowlands (Figure 5.1c). Minimum and maximum temperatures also show different patterns of seasonal variation. During the rainy months, maximum temperature declines while minimum temperature remains unchanged. After September, minimum temperature gradually falls to a minimum value in December, while, in contrast, maximum temperature increased after September to a peak in March.

Data transformation and imputation

To obtain approximate Normal distribution, log and cube-root transformations were applied to incidence and rainfall data, respectively. Monthly minimum and maximum temperature data were assumed to have Normal distribution. Prior to log transformation, a value of 1 was added to all monthly number of cases to avoid transformation problem which arises in the case of 0 values.

Before fitting models, missing values of rainfall and temperature were imputed using linear interpolation (for gaps of up to 5 months) or by taking seasonal average values (for gaps of more than 5 months). The value of a missing data point for month t (i.e. X_t) was estimated as:

$$X_t = \begin{cases} \overline{X}_t + X_{t-m} - \overline{X}_{t-m} + \dfrac{m(X_{t+n} - \overline{X}_{t+n} - X_{t-m} + \overline{X}_{t-m})}{m+n} & \text{if} \quad m+n \le 5 \\ \overline{X}_t & \text{otherwise,} \end{cases} \qquad (5.1)$$

where $\overline{X}_t$ is the seasonal average (of the transformed series) for the corresponding calendar month, m is the number of missing observations from the last observed value up to time t and n is the lead time to the next observed value in the 'future'. Of the data points relevant to the basic model (described below), the percentage imputed values of rainfall and minimum temperature were 12.7% and 15.8%, respectively.

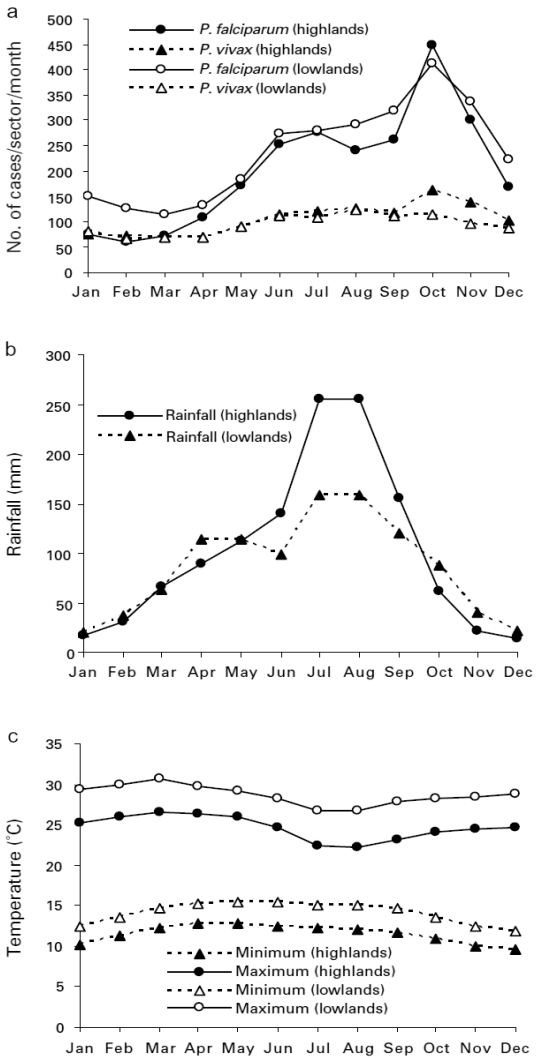

Figure 5.1 Seasonal variations in (a) incidence of *Plasmodium falciparum* and *P. vivax* malaria; (b) rainfall; and (c) temperature, in 'highlands' (>1750m) and 'lowlands' (≤1750m) in Ethiopia.

Theoretical Reasoning

In areas with low malaria endemicity, the number of new malaria cases in month t (denoted as I_t) can be considered to depend on the number of new cases in the previous month multiplied by the vectorial capacity during the previous month (vectorial capacity is defined as the average number of secondary malaria cases potentially disseminated in a susceptible population by vector mosquitoes per day from a single primary case). This is due to the fact that nearly all newly infected individuals develop clinical illness as a result of lack of immunity. In areas with high endemicity, many people are (partially) immune and (mostly) not clinically ill, but still infectious; only people who lack sufficient immunity would visit health facilities for treatment, and this means that the number of new cases is mainly determined by vectorial capacity in the previous month alone. The minimum generation time (sometimes referred to as the 'incubation interval' — i.e. the duration of a complete gametocyte-to-gametocyte cycle or the time from take-up of gametocytes by the vector until production of gametocytes by the next host after transmission), normally has a length of approximately one month in tropical temperatures, and this corresponds to the monthly character of the data used for analysis. These considerations can be generalized in the following equation:

$$I_t = aI_{t-1}^b C_{t-1}, \qquad (5.2)$$

where a and b are area-specific constants, and C_{t-1} is vectorial capacity in month $t-1$. If b is (close to) 0, we have $I_t = aC_{t-1}$ as expected in areas with high endemicity. On the other hand, if b is (close to) 1, we have $I_t = aI_{t-1}C_{t-1}$ as expected in areas with low endemicity.

C_t is defined as the product of mosquito density in relation to the human population (M_t) and vectorial capacity per mosquito (W_t) in month t:

$$C_t = M_t W_t. \qquad (5.3)$$

We assume M_t depends on rainfall during the previous 2 months and some area-specific constant M, and that there are enough mosquitoes present to generate an infinite number of offspring, whereby the presence of breeding sites is the limiting factor. Rainfall will be represented as amount during a particular month relative to average annual total for each area. Our assumption for taking rainfall relative to the annual total was that absolute rainfall is not so important but the consequences of rainfall in terms of number (and

duration) of mosquito breeding sites are important. These consequences differ strongly among areas (depending on vegetation, soil type, presence of rivers, topography etc.) and therefore there cannot be an absolute relationship between rainfall and vector abundance. For example, if absolute rainfall would be used then a doubling of rainfall in a relatively dry area would have relatively little impact, as the difference involved is small. Thus, the effects of this doubling would be underestimated. In a very wet area, these effects would be overestimated. Thus we have:

$$M_t = M \exp\left(\beta_1 \frac{R_{t-1}}{R} + \beta_2 \frac{R_{t-2}}{R} \right), \qquad (5.4)$$

where R_{t-1} and R_{t-2} denote rainfall in months t-1 and t-2, respectively, R is an area-specific average annual rainfall, and β_1 and β_2 are statistical coefficients of rainfall relative to annual total in months $t-1$ and $t-2$, respectively, to be estimated from data.

Vectorial capacity per mosquito W_t in eqn (5.3) was assumed to depend to a large extent on temperature, and was represented by the sum of a linear and a quadratic term of average minimum temperature (T) after a preliminary exploration of the likely effect of temperature; hence, we can write:

$$W_t = \exp(\beta_3 T_t + \beta_4 T_t^2), \qquad (5.5)$$

where β_3 and β_4 are statistical coefficients of T_t and T_t^2, respectively, to be estimated from data.

At higher temperatures, the sporogonic cycle of the malaria parasite within the mosquito would be shortened, increasing the probability of transmission (as the parasite would be more likely to be transmitted before the mosquito vector dies when the duration of the cycle is shortened). Temperature also has an effect on the length of the aquatic cycle of the mosquito, but in the present model, the effect on the parasite has been emphasized (and thus M_t assumed to depend entirely on rainfall as described in eqn (5.4)). In this regard, the effect of rainfall (a factor for mosquito production) was also made to precede that of temperature (a factor that acts on the parasite prior to transmission).

After substitution we get:

$$I_t = MaI_{t-1}^b \exp(\beta_1 \frac{R_{t-2}}{R} + \beta_2 \frac{R_{t-3}}{R}) \exp(\beta_3 T_{t-1} + \beta_4 T_{t-1}^2). \qquad (5.6)$$

Resulting statistical model

After taking (natural) logarithms, eqn (5.6) can be re-written as a linear mixed model for each sector *i* as follows:

$$\log(I_{t,i}) = \alpha_i + b_i \log(I_{t-1,i}) + \beta_1 \frac{R_{t-2,i}}{R_i} + \beta_2 \frac{R_{t-3,i}}{R_i} + \beta_3 T_{t-1,i} + \beta_4 T_{t-1,i}^2 + \varepsilon_{t,i}. \quad (5.7)$$

Here $\alpha_i = \log(M_i) + \log(a_i)$ denotes the sector-specific intercept, and $\varepsilon_{t,i}$ is a normally distributed random error with mean 0 and variance σ^2. This model describes the area-specific (log) incidence in month *t* as a function of: (1) (log) incidence in the previous month; (2) rainfall 2 and 3 months earlier; and (3) average minimum temperature in the previous month. In eqn (5.7), between-sector differences in average incidence and in the effect of previous incidence were accounted for by the random (sector-specific) intercept α_i and the slope b_i (i.e. parameter of previous incidence). The effects of rainfall and temperature were assumed identical across sectors. Using the MIXED procedure of the SAS/STAT® software of the SAS System Version 8.2 (SAS Institute Inc., Cary, NC 27513, USA), we estimated the intercept α_i and the slope b_i of $\log(I_{t-1,i})$ as sector-specific random effects, and $\beta_1, \beta_2, \beta_3$ and β_4, as fixed effects from the data (SAS Institute, Inc. 1999; Verbeke and Molenberghs 2000). This procedure can handle problems related to spatial and temporal autocorrelations in the data set during estimation of model coefficients and their variance.

In order to judge the quality of the predictions, the model was also extended to include more meteorological variables at different lags. Likelihood ratio tests were performed to test the goodness-of-fit of the various extensions in comparison to the basic model given in eqn (5.7). Also, variance as explained was used to reflect the goodness-of-fit per sector. Predictions were considered not good enough if they exceeded twice the observed values (over-estimation) or were less than half the observed values (under-estimation). Gross under-estimation in relation to missing epidemic events which was considered more important than over-estimation was also studied using a threshold value of 200 cases per month per sector, and the results were compared to other simpler models not using weather data, including a simple method using incidence of the previous month as a forecast value for the current month and a seasonal adjustment method that uses values of 3 previous months (Abeku *et al.* 2002).

5.4 Results

The estimates of coefficients in the basic model represented by eqn (5.7), estimated from data from the 35 sectors, are given in Table 5.2. All included effects were statistically highly significant except rainfall 3 months earlier which was significant at the 10% level. Area-specific intercepts and incidence in the previous month are given in Table 5.1. The area-specific effect of incidence in the previous month (i.e. term b_i in model (5.7)) showed little variation between sectors, with a mean of 0.72 (95% CI: 0.69–0.75). Three-quarters of the sectors have values of the coefficient between 0.65 and 0.80.

Observed and predicted values of the basic model are shown in Figure 5.2. The model produced similar percentages of over-estimation (19.7%) and under-estimation (18.6%). Especially high incidence values showed a good fit in the model. Detailed analysis of the under-estimation problem showed that about 10% of the observations were under-estimated by more than 200 cases per month, and about 5% were under-estimated by 400 cases per month. It was also found that sectors with normally high and low number of malaria cases had better fits than did sectors with moderate number of cases (Figure 5.3). For most areas, the amount of variance in incidence explained by the model exceeded 80%, and for nearly half of the 35 sectors this proportion exceeded 90%. The model performed better in areas with relatively high or low incidence (>85% of the variance explained) than in those with moderate incidence (55%-85% of the variance explained).

The various extensions of the basic model are given in Table 5.3 with their respective likelihood ratio tests for goodness-of-fit in comparison to the basic model. In general, there was no significant improvement when maximum temperature was included. Due to the fact that rainfall relative to annual total in the previous month, and the quadratic terms of rainfall relative to annual total 2 months and 3 months earlier significantly improved the model, these factors were used in an extended model which improved the model significantly (Table 5.3). However, in terms of prediction and percentage under- or over-estimated observations, virtually no improvement was obtained with the various extensions of the basic model, including the extended model.

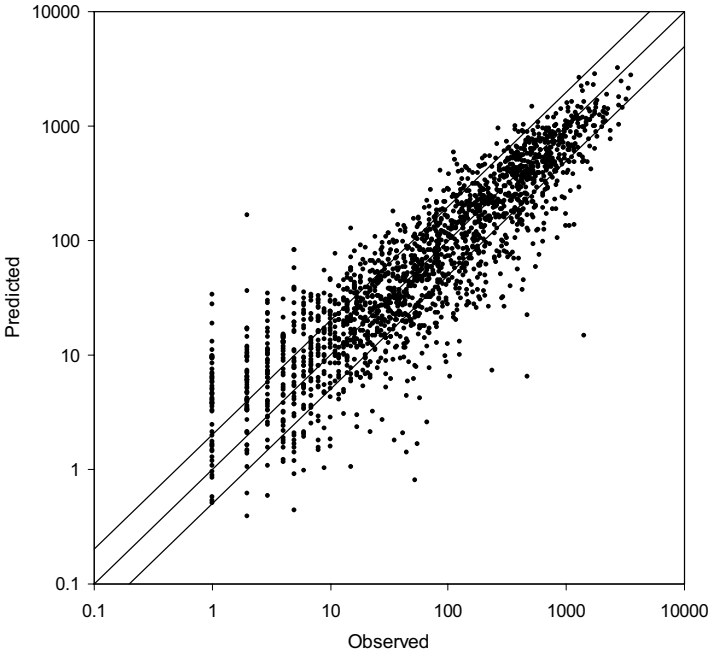

Figure 5.2 Goodness-of-fit of the linear mixed model: observed *vs* model-predicted values given in number of *Plasmodium falciparum* cases. Each dot represents a month and a site (n = 2,067). The diagonal parallel lines indicate prediction values twice observed values (upper line), equal to observed values (middle line) and half the observed values (lower line). (Of the predictions, 19.7% were twice the observed values and 18.6% were less than half of the observed values; furthermore, 10.2% of all observations were grossly underestimated — i.e. greater than 200 cases per month per sector).

Table 5.1 Characteristics of the 35 study areas (sectors) and area-specific random effects of the basic linear mixed model fitted to log-transformed *Plasmodium falciparum* incidence data reported during September 1986-August 1993.

Sector	Alti-tude (m)	Average daily temperature (oC)		Annual rainfall (mm)	Mean monthly no. of falciparum malaria cases	Intercept	Coefficient of Loge(incidence) in previous month
		Minimum	Maximum				
Abomsa	1800	15.3	28.2	960	706	-0.92	0.78
Adiszemen	1550	10.9	28.3	1315	63	-0.91	0.71
Alaba	1750	11.2	26.9	1032	252	-0.71	0.82
Alamata	1580	14.8	29.9	754	302	-1.13	0.77
Alemketema	2280	12.6	24.8	1174	30	-1.18	0.68
Ambo	2130	11.4	25.2	1024	6	-1.36	0.57
Arba Minch	1290	15.1	29.9	839	569	-0.92	0.75
Asela	2350	8.5	21.0	1208	264	-0.79	0.76
Awasa	1750	12.2	26.7	953	101	-1.05	0.69
Bahirdar	1770	11.5	26.6	1466	263	-0.79	0.76
Bati	1660	13.0	28.3	873	382	-1.12	0.80
Bedele	2030	12.0	25.2	1793	12	-1.20	0.50
Chagni	1620	12.3	27.7	1762	177	-0.96	0.75
Debretabor	2690	9.4	22.2	1565	65	-0.83	0.70
Debrezeit	1900	11.5	26.2	861	260	-1.00	0.79
Dembidolo	1850	13.0	25.0	1225	98	-0.81	0.64
Dila	1500	11.3	27.8	1323	26	-1.01	0.67
Fiche	2750	7.70	20.2	1211	40	-0.87	0.70
Finoteselam	1900	11.8	27.3	1129	96	-1.11	0.75
Gambela	480	18.6	35.8	1228	609	-1.02	0.76
Gode	295	22.5	34.8	262	44	-1.00	0.57
Harer	2100	13.5	25.2	713	276	-1.38	0.84
Hirna	2050	12.2	25.6	1041	14	-1.21	0.69
Hosana	2200	10.4	22.5	1186	37	-0.92	0.67
Jima	1725	11.1	26.9	1506	20	-1.13	0.67
Jinka	1480	15.7	27.0	1268	70	-1.15	0.68
Kombolcha	1903	11.8	25.9	1049	663	-1.33	0.86
Metehara	960	17.5	32.7	543	544	-0.82	0.73
Mizanteferi	1370	15.5	27.4	2180	44	-1.54	0.70
Nazret	1622	14.0	27.9	861	291	-0.95	0.75
Negele	1544	13.2	25.8	764	24	-1.19	0.65
Nekemte	2080	12.2	23.7	2089	130	-0.98	0.71
Sodo	2020	13.1	24.3	1263	370	-1.20	0.81
Weliso	2000	11.8	24.8	1203	106	-1.05	0.74
Zway	1640	13.5	26.4	757	426	-1.01	0.78

In terms of percentage of observations grossly under-estimated (>200 cases per month per sector), using the previous month's incidence as a prediction was surprisingly slightly better than the basic model (9.1% *vs* 10.2%). However, in terms of percentage of 'not good enough' predictions, the basic model performed better (38.3%) than the model using previous month's incidence (42.9%) (Table 5.4). The alternative model based on the seasonal adjustment method was slightly worse than both the basic model and the previous month's incidence prediction (Table 5.4).

5.5 Discussion

This study showed an association between monthly meteorological and malaria morbidity data in areas with unstable transmission using a statistical model based on theoretical reasoning. This linear mixed model, which includes rainfall 2 and 3 months earlier and mean minimum temperature in the previous month entered as fixed effects and incidence in previous month entered as a random effect, was fitted to malaria incidence data from 35 areas throughout Ethiopia. The model's fit was generally good especially in areas with high (and to some extent low) monthly incidence.

The model performed relatively poorly in areas with the mean number of cases per months between approximately 50 and 300. This may be due to the fact that only in high and low endemicity areas the immunological status of the population is constant (high and low, respectively). These observations indicate a need to incorporate in a prediction model dynamic or temporally varying immunity levels. Although the model was motivated using immunological arguments and takes account of spatial variations in communal immunity levels across areas, it does not incorporate varying levels of immunity over time, to handle, for example, a consequence of recent outbreaks on incidence. Nevertheless, the developed theory of varying immunity is speculative and needs further study. It should be noted also that incidence and immunity levels interact in such a way that one leads to the other and models for epidemic early warning need to include such interactions. In an attempt to incorporate the level of immunity in forecasting incidence, the spleen rate has been used as a proxy to immunity status of the population in epidemic early warning in India, although this approach did not appear to help in providing an adequate basis for accurate forecast (Swaroop 1949). In terms of prediction, the present model, however, performed better than our best model that was devised previously based on historical incidence patterns alone (Abeku *et al.* 2002). This indicates that weather variables are essential components in a model used for epidemic prediction. Potentially

confounding factors that affect transmission such as the level of drug resistant *P. falciparum* and the use of insecticides in malaria control in Ethiopia were ignored in the model, as (simple) prediction was our objective and the role of confounding factors was of less importance than in epidemiological studies of causation.

Table 5.2 Estimates of the fixed parameters of the basic linear mixed model fitted to log-transformed *Plasmodium falciparum* incidence data reported from 35 sectors in different parts of Ethiopia during September 1986-August 1993.

Effect	Estimate (S.E.)	*P*
Mean intercept (α)	-1.04 (0.22)	<0.0001
Mean log (*P. falciparum* incidence in previous month) (b)	0.72 (0.02)	<0.0001
Rainfall relative to annual total 2 months earlier (β_1)	4.12 (0.49)	<0.0001
Rainfall relative to annual total 3 months earlier (β_2)	0.81 (0.49)	0.098
Minimum temperature in previous month (β_3)	0.19 (0.03)	<0.0001
(Minimum temperature in previous month) squared (β_4)	-0.0045 (0.0012)	0.0001

The 95% CI for the estimates of the coefficient of incidence in the previous month (0.69–0.75) indicated a uniform value for most areas in the country. This is in concordance with the fact that most sectors in Ethiopia have similar endemicity levels. The individual effect of each of the predictor variables was investigated in the present study using model estimates for which the best fit was obtained, while keeping the other variables constant. Increased minimum temperature resulted in increase in incidence up to a threshold limit of approximately 23 ^{o}C, after which increase in minimum temperature ceased to have an effect on incidence. Around 14 ^{o}C, an increase in minimum temperature of 1 ^{o}C resulted in 8% increase in incidence. The exponential effect of rainfall associates with a 3% increase in incidence for every 1% increase in rainfall.

Table 5.3 Comparison of goodness-of-fit of the basic model to its extensions by adding more predictor variables (*n* = 2,067 and -2 log likelihood of basic model = 5,290.1).

Additional factor to the basic model	Estimate	S.E.	Test for significance of improvement over basic model	
			χ_1^2	*P*
Minimum temperature 2 months earlier	-0.0047	0.0149	9.3	0.002
Maximum temperature in the previous month	0.0048	0.0095	0.2	0.655
Maximum temperature 2 months earlier	0.0080	0.0099	0.6	0.439
Rainfall relative to annual total in the previous month	2.364	0.498	22.3	<0.001
(Rainfall relative to annual total 2 months earlier) squared	21.913	6.240	12.2	<0.001
(Rainfall relative to annual total 3 months earlier) squared	20.996	6.335	10.7	0.001

Although more detailed studies are still required to thoroughly understand the impact of meteorological variables in the genesis of epidemics in different areas, it seems that the effect of rainfall varies from sector to sector depending on prevailing temperature and other epidemiological factors. Previously, an inverse relationship was found between rainfall and incidence in southern Ethiopia in drought-associated epidemics due to breeding of vector mosquitoes in pools formed in river beds and streams (unpublished data). Abnormally high rainfall is causative factor for epidemics in lowlands and fringe areas bordering lowlands. In the cooler highlands, temperature (especially minimum temperature) has a more profound role in determining malaria transmission. A drop in temperature has been shown to be associated

with interruption of transmission in the highland sectors of Ethiopia (Abeku *et al.* 2003). In the hypoendemic highlands, temperature exerts its effect on transmission mainly as the result of shortened sporogonic cycle of the parasite within the vector, and to some extent also by accelerating larval development and frequency of blood feeding by the vector.

Table 5.4 Comparison of different models in terms of percentage of 'unacceptable' predictions (greater than twice or less than half observed values) and percentage of observations grossly underestimated (i.e. greater than 200 cases per month) (n = 2,067). (The seasonal adjustment model was based on (Abeku *et al.* 2002).)

Model	Predictions >twice observed values (%)	Predictions <half observed values (%)	Observations grossly underestimated (>200 cases per month) (%)
Basic model [7]	19.7	18.6	10.2
Extended model	19.2	18.0	9.7
Alternative model: current month's incidence = previous month's incidence	22.0	20.9	9.1
Alternative model: seasonal adjustment	21.3	24.0	11.1

In a study conducted in Rwanda, Loevinsohn (1994) showed that changes in malaria incidence at health facilities were significantly associated with rainfall while temperature predicted incidence best at higher altitudes. It was shown that a model that included log of minimum temperature 1 and 2 months earlier, and rainfall 2 and 3 months earlier fitted the health facility data adequately. In our study minimum temperature in the previous month included with its quadratic term usually gave adequate fits in the presence of the previous month's incidence level. Incidence was not included as a predictor variable in the Rwandan study, but in our model we have shown that it is

highly significant as a determinant of incidence in the following month. Previously, we have shown that malaria epidemics in Ethiopia were significantly more often preceded by a month of abnormally high minimum temperature in the preceding three months than based on random chance (Abeku *et al.* 2003). In another observation made in Zimbabwe, Freeman & Bradley (1996) reported that rainfall has little effect on severity of malaria (assessed by comparing the numbers of malaria deaths and malaria-inpatients in any one year with respect to those in the preceding years), while temperature has an effect. In Uganda, Kilian *et al*. (1999) reported the existence of a close correlation between peak of rainfall and peak of malaria incidence with a time lag of 2-3 months between them. In a study conducted in central Ethiopia, Tulu (1996) reported that a rise in monthly mean minimum temperatures 2 and 3 months earlier was the strongest predictor of a rise in incidence. In the present study, the inclusion of minimum temperature of 2 or 3 months earlier did not improve the basic model and the effects were not significant whereas the effect of minimum temperature of previous month (already in the model) was strongly significant.

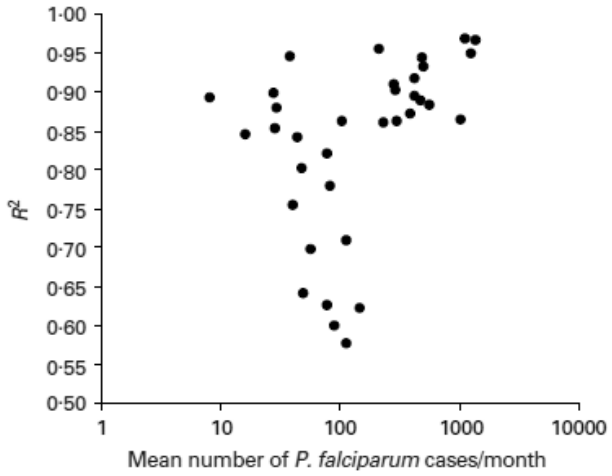

Figure 5.3 Goodness-of-fit of the model (measured in R^2 values) as a function of mean monthly number of *Plasmodium falciparum* cases in each sector.

To test whether changes in the weather variables have different effects on incidence in highlands and lowlands, we carried out a stratified analysis by dichotomizing altitude into high (>1,750m) and low (≤1,750m) and including in the model interaction terms between meteorological and the dichotomized altitude variables. The altitude variable and all the interactions with the weather variables did not have significant coefficients, and the inclusions did not improve the basic model; the main results of the study remained unchanged. This is probably due to either absence of difference in effects of meteorological variables at different altitudes or due to the already included temperature variables in the model as temperature is strongly negatively correlated with altitude, thus indirectly taking account of the effect of altitude.

Climate-based distribution of malaria transmission and infection risk models for Africa has been proposed (Craig *et al.* 1999) and spatially predictive models have been prepared for epidemic-affected areas of Africa (Cox *et al.* 1999). The present study has indicated how the association between some meteorological factors and incidence may be modeled in a continuing effort to develop epidemic early warning systems in highland areas for temporal prediction.

Satellite-derived remote sensing (RS) data are potentially useful for monitoring malaria epidemics, although in some cases they may not provide accurate spatial proxies to actual ground meteorological measurements. The relative accuracy of RS and spatial interpolation (SI) of data from meteorological stations has been assessed for the prediction of spatial variation in monthly climate across Africa (Hay and Lennon 1999). It has been found that SI was a more accurate predictor of temperature, whereas RS provided better surrogate for rainfall. On the other hand, it has been shown that Normalized Difference Vegetation Index (NDVI) in the previous month correlated consistently with malaria incidence across three sites in Kenya (Hay *et al.* 1998). Although there is obviously no direct causal link between NDVI and malaria cases to use it as a variable in the current model, the relationships between this and other RS data, ground meteorological records and malaria incidence in the highlands need to be further investigated, for possible use in similar models. A detailed study has been initiated to investigate such relationships with epidemic malaria in four highland districts in Kenya and Uganda, as part of the Highland Malaria Project (HIMAL) (www.himal.uk.net).

The present analysis showed that a statistical model based on theoretical reasoning is a good starting point to understand the role of abnormal weather variables in triggering epidemics in the highlands or highland fringe areas, and

that the impact of the effects of these variables in terms of morbidity outcomes may depend on several factors including communal immunity and number of pre-epidemic parasite reservoirs in the population.

Prediction of incidence several months in advance will require major adaptation of the current model, for example, by making use of predicted values of the predictor variables themselves. However, it is anticipated that the accuracy of such prediction would deteriorate after a few months, compared to the (already moderate) performance of one month prediction. Further validation is also needed by fitting the model to new data sets to estimate random effects by using optimal estimates of the fixed parameters. Ways to improve forecasts by making use of past patterns of incidence and other variables and/or by combining seasonality and weighted forecasts of different methods in relation to population immunity levels are currently under investigation. In terms of prediction of malaria incidence using the basic model, although the main contribution comes from previous month's incidence, the weather parameters included are highly significant and values of their coefficients meet our expectations. Also, we have demonstrated that inclusion of maximum temperature is not important at all. Nevertheless, the study shows that prediction rules derived from simple and straightforward use of monthly weather variables alone might not produce accurate forecasts. In addition, it may be important to study the weather-malaria relationships in some more details using time series of weather, morbidity and entomological variables at intervals of less than a month. The modelling approach used in this study has shown the most important variables that need to be considered in developing a malaria epidemic early warning system in areas where communities are at risk of sudden increase in transmission due to slight changes in the precipitating factors.

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6

Response to malaria epidemics: available options and associated challenges

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Submitted

6.1 Summary

Malaria epidemics affect many highland and semi-arid areas, often resulting in high morbidity and mortality of the largely non-immune populations. Most interventions to prevent or contain epidemics are associated with challenges facing countries with limited resources. Effective prevention is particularly difficult in the highlands, where predictive accuracy of indicators is not sufficiently high to allow decisions involving expensive preventive measures such as indoor residual spraying of insecticides. Current advances in geographical information systems have proved useful in stratification of highland areas to guide selective targeting of interventions, including barrier application of insecticides in transmission foci to protect spread of infection. In arid areas, early warning methods based on seasonal climate predictions have been recently proposed based on a strong association between rainfall and epidemic events. Response to malaria epidemics should focus on early recognition of epidemics and rapid deployment of mass drug administration or mass fever treatment using relatively inexpensive artemisinin-based combination antimalarials such as artesunate-amodiaquine. Vector control measures including indoor residual spraying should be recommended only if abnormal transmission is anticipated with high probability and if such measures can be selectively implemented at an early stage of an outbreak.

6.2 Introduction

Epidemic malaria continues to be a major threat to several areas in Africa, the Americas, Asia, and some parts of the Middle East (Nájera *et al.* 1998; WHO/RBM 2001). The most affected regions are highlands and arid areas where populations lack effective immunity. Rapid response is essential to reduce the adverse consequences of epidemics. This is possible where effective surveillance systems are in place for close monitoring of disease incidence for early recognition of anomalous situations.

Early warning systems prior to the stages when increases in disease incidence are obvious may potentially be useful to reduce disease burden resulting from epidemics. However, there are a number of challenges associated with the accuracy of early warning or detection methods, and the associated decisions on interventions. These will be discussed in subsequent sections within the context of current research findings relevant to epidemic malaria and capacities of epidemic-prone countries in implementing the interventions.

6.3 Highlands and semi-arid areas

Areas that are usually at risk of malaria epidemics can be classified as either highlands or (semi-) arid desert fringes. In most cases, epidemics follow abnormal weather conditions, often in combination with other causes, including increased resistance of the parasite to antimalarial drugs, population movement due to seasonal labour and civil unrest, and reduced malaria control operations, in particular the cessation of regular vector control (Molineaux 1988).

In highland areas, transmission is unstable due to fluctuations in temperatures which are normally low (Cox *et al.* 1999). Temperature affects the duration of the sporogonic development of the *Plasmodium* parasite within the *Anopheles* vector and the development, survival and feeding frequency of the vector. Most of the epidemics affecting highlands that support short, annual, transmission are superimposed over normal seasonal increases, a phenomenon that makes early detection difficult. Other areas experience occasional transmission in specific years with more pronounced levels of morbidity and mortality, and significant spatial and temporal variations (Abeku *et al.* 2003). On top of the explosive epidemics, highland areas in Africa have also exhibited an increasing trend of malaria transmission in recent years (Shanks *et al.* 2000). This trend has significant implications for choosing response mechanisms.

Arid or desert fringe areas are characterized by warm climate, and abnormal malaria transmission is associated with anomalous rainfall causing increased vector breeding and survival. In Botswana, more than two-thirds of the variability observed between years in malaria incidence during January-May could be explained by variation in rainfall during December-February (Thomson *et al.* 2005). A major epidemic that affected arid areas in north-eastern Kenya in January-May 1998 was shown to have been caused by abnormal rainfall and floods during November-December 1997 (Brown *et al.* 1998). In these areas, monitoring of rainfall can provide a fairly accurate forecast of transmission risk (Grover-Kopec *et al.* 2005; Thomson *et al.* 2005; Thomson *et al.* 2006).

6.4 Preventive interventions

Response actions can be triggered following early warning or detection signals at different lead times, ranging from months to weeks, based on the nature of the indicators used (WHO/RBM 2001; WHO 2004). The type and targets of interventions depend on the forecast probability, available resources and the timing of the events or available lead time. In most cases, highly accurate forecast is not possible as yet (e.g. in highlands); hence emphasis should be placed on improving surveillance for early detection of abnormal incidence to minimize delays in responding (Teklehaimanot *et al.* 2004).

Control programmes are usually faced with uncertainties regarding decisions on whether routine (seasonal) preventive measures should be employed in areas known to be at risk due to their geographic characteristics, or alternatively, whether developing mechanisms for rapid response is a better strategy. In epidemic situations, sound decisions have to be made rapidly, while at the same time resources have to be used economically. Regular IRS on a yearly basis may be an unnecessary waste of resources in most highlands with substantial inter-annual variability of incidence. The obvious issue in applying IRS on an annual basis is therefore weighing the risk of wasting expensive resources against the probability of abnormal transmission. In Madagascar, annual IRS was restored during 1993-98 to reverse the spread of epidemic malaria that reappeared following re-colonization of the central highlands by *A. funestus*, which previously disappeared following effective control campaigns (Jambou *et al.* 2001; Curtis 2002; Romi *et al.* 2002). After 5 years of spraying DDT mostly in areas between 1000 m and 1500 m altitude, vector density and malaria prevalence rates were significantly reduced. Annual IRS campaigns in the 1950s in the epidemic-affected highlands of Kenya have also produced similar results (Roberts 1964; Roberts 1964). Planning selective application of insecticides for a limited number of

years in areas most at risk of unstable transmission, followed by focal use as and when required, is probably worth considering, in particular in areas bordering endemic lowlands or in transmission foci in valleys in the highlands.

Valleys in highlands have been repeatedly shown to be the source of infection for surrounding populations in a number of studies. A survey in an altitudinal transect in the Usambara mountains in Tanzania has shown the importance of local topography in explaining variations in splenomegaly among residents (Balls *et al.* 2004). Not surprisingly, altitude correctly predicted 73% of households where an occupant had an enlarged spleen or not. Inclusion of land where water is likely to accumulate within 400 m of each household significantly improved predictions in areas between 1000 m and 1200 m altitude where malaria is unstable. In western Kenyan highlands, indoor density of vectors has been shown to be negatively associated with distance from swamps (Minakawa *et al.* 2004). On the other hand, human activities such as brick-making have created important breeding sites for anopheline vectors (Carlson *et al.* 2004). A spatial analysis of the distribution of *P. falciparum* in the highlands of Kenya has indicated that prevalence of infection and parasite densities both decreased with distance from the valley bottoms (Munyekenye *et al.* 2005). These foci maintain low levels of transmission through the dry periods and are a potential source of infection when weather and other conditions favour widespread outbreaks in surrounding highlands. Selective (annual) spraying of these valley bottoms and areas in the vicinity of man-made transmission sources may provide protection to the populations in the highlands.

The potential use of geographical information systems (GIS) and remote sensing (RS) techniques to map transmission foci and risk factors and to guide targeting of interventions has been extensively reviewed (Hay *et al.* 2000; Myers *et al.* 2000). Spatial epidemic risk maps have been proposed for highland areas in the Horn of Africa and East Africa based on the climate profiles of epidemic-affected localities (Cox *et al.* 1999). Although static spatial maps are useful for general stratification of areas and have been used to design regular interventions (e.g. annual IRS) in countries such as Madagascar (Jambou *et al.* 2001), South Africa (Booman *et al.* 2000) and India (Singh *et al.* 1990), different geographic areas have been shown to be at risk of epidemics in different years based on prevailing conditions (Abeku *et al.* 2003).

Several international collaborative efforts have been initiated in the past few years to develop and test temporal risk maps based on rainfall anomalies using remote sensing technologies, with special applicability in arid areas (WHO 2002; Grover-Kopec *et al.* 2005). Rainfall anomaly maps that are

continually updated every 10 days are now available over the Internet from the web sites of the Famine Early Warning Systems Africa Data Dissemination Service (http://igskmncnwb015.cr.usgs.gov/adds/) and the International Research Institute for Climate and Society http://iridl.ldeo.columbia.edu/maproom/.Health/.Regional/.Africa/.Malaria/). The operational use of these technologies for early warning of transmission and selective application of preventive interventions and preparedness interventions is yet to be fully evaluated, although encouraging results have been documented in southern Africa, especially in Botswana (WHO 2002; DaSilva *et al.* 2004; Grover-Kopec *et al.* 2005). Following the high predictability of inter-annual variations in malaria incidence provided by rainfall variability in Botswana (Thomson *et al.* 2005), an early warning system with a longer lead time was proposed, which provides probabilistic forecasts of anomalously high or low incidence in the desert-fringe setting based on seasonal precipitation forecasts from a multi-model ensemble climate predictions (Thomson *et al.* 2006). Although it has been claimed that the system can add up to four months of warning over methods using observed precipitation, its sustainable applicability to target preventive measures remains to be seen.

In highlands, monitoring temperature anomaly can provide crude forecasts. Studies carried out using data from Ethiopia indicate that major epidemics in the 1980s and early 1990s were significantly more often preceded by a month of abnormally high minimum temperature during three months before the onsets than would be expected by random chance (Abeku *et al.* 2003). Similarly, in Zimbabwe, temperature was found to be associated with severity of epidemics (Freeman and Bradley 1996). Studies involving concomitant longitudinal follow-up of weather patterns, vector densities and malaria incidence are currently on-going in highland sites in Kenya and Uganda to describe the mechanisms of epidemics (Abeku *et al.* 2004).

On the other hand, a number of studies have shown the association of epidemic malaria with El Niño Southern Oscillation (ENSO) events in many parts of the world (Kovats *et al.* 2003). For example, analysis of malaria data from Colombia for the period 1980-1997 appears to indicate that El Niño events intensify the annual seasonal transmission cycle (Poveda *et al.* 2001). Prediction based on ENSO indicators may prove useful for the purpose of ensuring availability of resources at national levels, in particular drugs and insecticides, as it provides relatively long lead times (WHO 2004).

6.5 Rapid assessment

Capacity to detect abnormal transmission at its early stages is essential for effective and rapid containment of epidemics. An important aspect of such a capacity is the existence of an efficient disease surveillance system. It has been demonstrated that a computer-assisted, weekly sentinel surveillance can be set up at district levels and early detection of epidemic events is technically feasible (Abeku *et al.* 2004).

Preparatory actions that have to precede the actual interventions include confirmation of the outbreak reports, assessing the magnitude and geographical extent of the increase, prioritising areas, and deciding on the types of interventions required. These steps, however trivial they might seem, are nevertheless essential and have to be taken within the shortest possible time. In most cases, simple rapid assessment methods are sufficient to make the necessary decisions. As an example, in an epidemic that affected Uasin Gishu District in Kenya, school absenteeism was used as an indicator to determine priority areas for mass fever treatment (Some 1994).

More advanced techniques that are economical, powerful and rapid can also be implemented, especially if sampling procedures are adopted in advance of an epidemic event. Lot quality assurance sampling (LQAS) with single- and double-sampling plans has been proposed for surveys involving determination of interventions in communities that deserve priority actions in terms of their disease prevalence (Lemeshow and Taber 1991). This method involves choosing a combination of sample sizes and a critical prevalence level beyond which an intervention is recommended, with the required statistical power and critical level. For example, in Madagascar, this procedure was tested by comparing it to a conventional sampling plan to select areas where prevalence rate among school children was $\geq 15\%$ [1], in which case the area was to be a candidate for some specific action (Rabarijaona *et al.* 2001). A plan in which 2 individuals were found positive among a random sample of 36, denoted as (36,2), classified communities correctly with 100% sensitivity and 94% specificity. Rapid diagnostic tests (RDTs) can be used in such surveys (WHO 2004).

The use of IRS for epidemic control should only be considered if continuation of transmission is anticipated over a long period (e.g. epidemics that occur before the rainy season or at the start of the transmission season)

[1] A second threshold value of $< 5\%$ was also used to determine areas with low prevalence.

and if it can be implemented rapidly at the early phase of an epidemic. However, the main challenge is that, currently, few countries have the capacity to organize and implement IRS.

There is no sufficient evidence to use insecticide-treated nets (ITNs) for epidemic prevention and control, so their use is limited to situations where their availability and rapid implementation is possible — such as in refugee camps (WHO 2004). Larval control may have a limited role in some situations, for example, in arid areas, with well-defined mosquito breeding sites after rainy periods, or in man-made sites such as wells and water storage tanks. Larviciding is probably effective where water bodies cannot be eliminated due to essential economic activities such brick-making (Carlson *et al.* 2004).

Occasionally, widespread epidemics affect large geographical areas such as those experienced in the highlands of Ethiopia (Fontaine *et al.* 1961; Abeku *et al.* 2003). In such situations, it would be difficult, if not impossible, to carry out a large scale preventive IRS operations even if an early warning system is in operation. Health services need to focus on more feasible measures such as strengthening preparedness by stocking drugs and diagnostic materials, close monitoring of changes in morbidity, sensitising communities to seek prompt treatment, classifying areas according to their risk levels and making contingency plans to rapidly deploy mobile treatment teams.

6.6 Mass drug administration and mass fever treatment

Mass drug administration (MDA) is the presumptive treatment of the entire affected population with a therapeutic dose of an antimalarial, whereas mass fever treatment (MFT) refers to treatment of febrile cases only. These approaches usually involve deployment of mobile treatment teams in affected areas, and availability of sufficient and appropriate antimalarials.

Where reliable early warning systems are not in place due to technical, logistics or other reasons, stocking of contingency antimalarials in health units across areas at risk prior to known transmission seasons can be an alternative approach. Epidemics tend to occur during those seasons, which mostly follow the rainy period (Abeku *et al*. 2003). Areas historically known to be most at risk should be identified from reports and/or based on suitability of environmental characteristics for unstable transmission to prioritize health units for drug distribution. If available, spatial maps may be utilised for classification of areas, including those of the MARA (Mapping Malaria Risk in Africa) or Highland Malaria Projects (Cox *et al.* 1999; Craig *et al.* 1999). In the absence of usable maps, there are proposed proxy measures such as adult-to-child ratios of patients attending health facilities, especially admission

cases. This approach has been used in Kenya to study stability of malaria in the highlands (Hay *et al.* 2002). Admission cases were classified into two age groups: below 15 years of age ('children') and 15 years and above ('adults'). Based on the age structure of the developing country populations, the adult-to-child ratio of hospital admissions approached unity for an unstable malaria situation, where adults are as likely as children to be at risk of severe and complicated malaria.

MDA has been used alone or in combination with IRS for the prevention and control of malaria in various settings. The primary objective of this measure in epidemic control context is to reduce the human reservoirs of the parasite by reducing infectiousness to vectors, while providing at the same time curative and prophylactic benefits to treated individuals. Antimalarials or combinations of antimalarials with schizontocidal and gametocytocidal effects should be used to have the desired effects on transmission. In the past, primaquine was given in combination with 4-aminoquinolines for its effect on gametocytes. In an endemic area in Tanganyika (part of the present day Tanzania), the repeated use of amodiaquine and primaquine combination significantly brought down transmission by reducing the sporozoite rates (Clyde 1961). Repeated MDA with proguanil, a prophylactic antimalarial with gametocytocidal activity, has been shown to have a significant impact on transmission in the highlands of western Kenya in the late 1940s (Strangways-Dixon 1950). Although many MDA trials failed to interrupt transmission, most succeeded in considerable reduction in parasite prevalence, and some showed marked transient effects on morbidity and mortality (von Seidlein and Greenwood 2003). There were, however, deficiencies in study design, as many of the early studies relied on comparing intervention and control villages of insufficient sample sizes.

On the other hand, using MFT as an important rapid measure has been proposed for epidemic control rather than using MDA for the entire population (WHO 2004). Attaining a high coverage is crucial, and epidemiologically relevant questions in this regard include the practicality of diagnosing fever cases in emergency situations and whether a large enough proportion of the population can be treated in this way so as to have a considerable impact on transmission. In Ethiopia, the Ministry of Health guidelines recommend rapid sampling of households and determining the proportion of occupants with illness in the previous seven days; a cut-off value of 50% would then be used to decide whether to employ MFT or MDA (Abose *et al.* 1999).

Recently, the introduction of combination therapy with artemisinin derivatives, which have been shown to have gametocytocidal effects led to the hypothesis that their use for MDA on a large scale might be a potential

malaria control measure (von Seidlein and Greenwood 2003). Artemisinin-based combination therapy (ACT) drugs have been shown to have a moderate effect on transmission by reducing the duration of gametocyte carriage and the proportion of mosquitoes that are infected by carriers (Bousema *et al.* 2006). In The Gambia, children treated with the combination of chloroquine (CQ) and artesunate (AS) were significantly less infectious to mosquitoes than children treated with CQ alone (Drakeley *et al.* 2004). It was also found that treatment with the combination containing AS significantly reduced the prevalence and density of gametocytes, as well as the duration of gametocyte carriage, although the effect was transient as it did not prevent emergence of mature gametocytes at day 28 following treatment (Drakeley *et al.* 2004). Another study in an area with highly seasonal but intense transmission in The Gambia showed that MDA with a single dose of AS combined with sulfadoxine-pyrimethamine (SP) failed to interrupt transmission overall but incidence in treated villages was significantly lower than in the control villages in the first two months (von Seidlein *et al.* 2003). This failure of MDA to interrupt transmission was attributed to the high entomological inoculation rate in the area. Nevertheless, it appears that MDA with a full therapeutic dose of ACT can play a major role in the control of epidemics and in the control of malaria in areas with short transmission season (von Seidlein and Greenwood 2003).

Treatment of fever cases, whether at health facilities or in epidemic control, presents the challenge of balancing costs in time and other resources on the one hand and accuracy of clinical diagnosis on the other. This diagnostic method is particularly less accurate in areas of low endemicity compared to highly endemic areas (Chandramohan *et al.* 2001), although there is a tendency of an increase in sensitivity and specificity during transmission seasons (Muhe *et al.* 1999). As a result, over-diagnosis of malaria in areas of low transmission remains a major problem, especially when expensive ACT drugs are to be used for treatment of fever cases. Furthermore, surveillance systems that rely entirely on data generated from health facilities without laboratory confirmation can lead to false epidemic alerts (unpublished data).

RDTs can be easily implemented in field conditions with minimal training. Their cost-effectiveness in epidemic situations in relation to the use of ACT has been recently compared with presumptive treatment using a model based on actual cost data (Rolland *et al.* 2006). The study showed that the threshold prevalence beyond which the RDT-based treatment becomes more expensive than presumptive treatment is 21% for artesunate-amodiaquine (AS-AQ) and 55% for artemether-lumefantrine. During epidemics, the percentage of highland populations infected or incubating infection is usually higher than the threshold for AS-AQ. A recent study in

western Kenyan highlands showed that nearly 44% of the sampled population were infected over a 10-week period during an epidemic, with adults and children similarly affected (John *et al.* 2004). These observations indicate that relatively less expensive ACT drugs such as AS-AQ can be cost-effectively used in MFT without laboratory confirmation. For large scale epidemics when most of the population are either infectious or incubating the infection, MDA with such relatively cheaper ACT distributed once or repeated within 1-2 weeks can have a significant impact on transmission.

The choice of treatment sites largely depends on the magnitude of the epidemic. Treatment at existing health facilities should be given special attention, and national and district health services should ensure that essential drugs for the treatment of both uncomplicated and severe malaria are in stock. In many situations, mobile treatment centres will be required to cover rural areas far from health facilities. It has been demonstrated that rapid deployment of manpower and logistics is feasible once the appropriate resources are in place, as in, for example western Kenya, where mobile treatment teams could be assembled in one week through a provincial health system to control an outbreak in Uasin Gishu District (Some 1994).

6.7 Conclusion

Malaria epidemic prevention and control requires rapid and coordinated efforts. While many countries still need to improve their technical and logistics capacity to deal with high demands in resources, recent technological advances in spatial analysis and risk-mapping, availability of satellite-derived rainfall estimates and anomalies, computer-assisted surveillance systems and effective antimalarials should be utilised for better targeting of interventions to effectively contain epidemics. In arid areas, early warning methods using actual or probabilistic prediction of seasonal climate have been proposed for implementation of prevention measures. Research is on-going to develop better predictive models for epidemics in highland areas, but monitoring anomalies in weather patterns, especially minimum temperatures, may provide good indicators. IRS and other vector control measures may be used in special situations where selective and timely application is feasible. The use of relatively inexpensive ACT drugs such as AS-AM in MDA or MFT should be a primary strategy for rapid transmission reduction in epidemic situations.

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7

General discussion

The main objectives of this thesis were to understand the environmental factors that trigger malaria epidemics, to test methods of epidemic forecast, to develop a new surveillance system for early detection of epidemics, and to discuss and recommend epidemic response strategies suitable for areas at risk of unstable transmission. We focused on African highlands, paying particular attention to three countries: Ethiopia, Kenya and Uganda.

In receptive highland areas, epidemic malaria characteristically exhibits a dramatic increase in morbidity and mortality, leaving little time to organize response measures by health services unless a strong surveillance mechanism is in place for early recognition of abnormal transmission. Detection of epidemics in their early stages is an important service that needs to be set up in areas known to be at risk of unstable transmission. Furthermore, effective preventive measures are possible only if there are systems that would help health services to anticipate abnormal transmission.

In subsequent sections, we will discuss how the research questions posed under Chapter 1 were addressed in the studies carried out as part of this thesis. Results of some additional analyses of data collected from epidemic-prone areas will also be presented. We will answer the research questions in the light of the findings and discuss their implications within the overall context of research on epidemic surveillance and response. We will also present additional results related to some of the challenges of setting up sentinel surveillance systems and studies on proxy measures for dynamic communal immunity and their potential use in incidence prediction models. Due to the implications of the current upward trends of malaria in some areas, we will discuss the impact of long-term climate change and climate variability on malaria in the highlands. Finally, we will provide general conclusions and recommendations in relation to epidemic prediction, detection, preparedness, prevention and control.

7.1 Answering the research questions

What is the state of the art of malaria epidemic early warning and the potential use of computer-based sentinel surveillance for early detection?

There has been a significant progress in the development of malaria epidemic early warning systems, and especially detection of epidemics at their early stages is technically feasible using computer-based sentinel surveillance (Chapter 2). We have described a new district-based sentinel surveillance system comprising weekly reporting and automated analysis which we have been piloting in four East African highland districts. As part of this

computerized system, we developed a new algorithm for the detection of abnormal incidence after removing trends from the baseline. The site-specific expected incidence and threshold values are allowed to change from week to week based on seasonality of transmission and from year to year based on underlying trends. The baseline is also allowed to be dynamically changing in length as more data is realized, resulting in a novel approach to detect anomalies even in the presence of potential biases such as gradual changes in the number of patients presenting at sentinel sites, which are not directly related to changes in transmission intensity and may be caused by other factors including new health units in the vicinity of the sites or changes in population density.

The system has the capacity to produce automated analysis reports on a weekly basis which can then be readily viewed by health staff at district levels and used for action. Analysis and interpretation of surveillance data has been decentralized and computer-generated reports are disseminated by the district health management teams to stakeholders including central level Ministries of Health. The previous surveillance systems of epidemic diseases in most countries relied on transmission of manually compiled data to central Ministries of Health, which were hardly used for early detection of outbreaks due to severe delays in delivery of reports and analyses. We introduced a weekly system of reporting and analysis to increase the sensitivity of the epidemic detection system for timely control measures. The use of data from a few selected sentinel sites rather than too many sites (some of which might have similar epidemiological characteristics) also increased efficiency in terms of data entry and supervision for quality control. The selected sites are supposed to deliver weekly reports consisting of daily outpatient and inpatient data to the district level where they are entered into a computer for comprehensive automated analysis.

The performance of different statistical methods has been compared in terms of their sensitivity and specificity in epidemic detection (Hay *et al.* 2002). None of the previously implemented methods possess some of the important features of the new system, especially those related to de-trending of the temporally changing baseline data. One of the main technical constraints of the new system is the accuracy of clinical diagnosis of malaria cases, as it is based on data generated through this process rather than the scanty data on microscopically confirmed cases. The potential use of the rapid diagnostic tests in sentinel sites for surveillance purposes should be further investigated to address this issue. The system also requires some set-up costs in each epidemic prone district, including compilation of baseline data and installation of computer hardware and software.

Developing the technical and logistical capacity of districts to optimally use the data collected at selected health facilities, essential for timely recognition of abnormal transmission and taking prompt action, has been shown to be feasible. Ways of integrating the new approach with the overall epidemic disease surveillance activities in the health services and its wider scale implementation is being explored.

Developing epidemic forecast capacities of countries where preparedness and preventive measures can reduce the morbidity and mortality burden resulting from unstable transmission remains to be a major focus from public health point of view. The effectiveness of epidemic response measures depends on the degree of preparedness of health services to detect abnormal signals, the actual lead time left for taking control measures and their capacity for implementation within the remaining time (Nájera 1999). Practical epidemic forecasting on the basis of scientific studies was probably implemented first in India in the 1920s and 1930s (Swaroop 1949). The forecasting method developed by C. A. Gill was based on information pertaining to rainfall, enlargement of spleen among school children, economic conditions and the variability of incidence in individual localities recorded in previous years.

Research is still on-going to develop robust forecast models based on environmental variables. The use of climate forecasts, rather than observed weather data, would give longer lead times for preparedness. However, it has been claimed that seasonal climate forecasts did not anticipate heavy rainfall which preceded an epidemic in the western Kenyan highlands in 2002 (Hay *et al.* 2003). Accuracy of seasonal climate forecasts varies according to geographical region, season and year, and such forecasts cannot be completely accurate and should always be issued in probabilistic terms as above, below, or near normal (Thomson *et al.* 2003). More recently, a system of forecasting probabilities of anomalously high and low incidence of malaria based on seasonal climate predictions has been implemented in Botswana (Thomson *et al.* 2006).

As part of the HIMAL Project, high temporal resolution data on confirmed cases of *P. falciparum* malaria, entomological parameters including indoor densities of the main vectors and meteorological data have been collected on a longitudinal basis to closely study factors responsible for triggering epidemic malaria in the highlands. Detailed statistical studies are being carried out on the associations between these parameters and their interactions with dynamic communal immunity, to develop incidence prediction models which could be used for dynamic risk mapping.

How helpful are time series methods in forecasting malaria epidemics?

A relatively simple time series method based on adding to "future" expected seasonal values the average deviation of incidence during the previous three months from month-specific expected means gave the most accurate forecasts, especially when the means were calculated based on three years of baseline data (Chapter 3). We presented a comparative study of using various time series methods for forecasting incidence of cases. Statistical sophistication was found to be not always desirable and may, contrary to expectations, lead to inferior performance in terms of accuracy when past morbidity patterns alone are used for forecasting. We found that a special seasonal adjustment method produced better forecasts compared to the more advanced ARIMA technique. This is most probably due to over-fitting of data, which means that simpler methods are robust to slight chance variations. The best-performing seasonal adjustment method uses the expected mean for any specific month together with the average deviation of the observed incidence values during the last three months from their expected values.

Like all univariate methods, the so-called Box-Jenkins approach (Box and Jenkins 1976) to time series analysis (or ARIMA modelling) does not take into account the biological basis of the process that gave rise to a series. It is rather based on attempts to identify best-fitting models to describe a past pattern. One of the basic assumptions is that the past pattern will not change during the forecast period. This assumption cannot always be met. On the other hand, most malaria series have strong seasonal components which can be adequately handled by ARIMA models through seasonal differencing. As stationarity is an essential requirement in building ARIMA models, most malaria series are made stationary after applying both seasonal and lag-1 differencing. However, differencing can have a great effect on the behaviour of the forecasts. It has been observed that for seasonally differenced data with lag-1 differencing, the long-range forecasts will follow a linear trend, extrapolating the trend at the end of the data series if no constant was fitted (Makridakis *et al.* 1998). If the constant has been included, the long-range forecasts will follow a quadratic trend. In either case, the forecast variances will diverge very quickly and as a result, prediction intervals will also diverge quickly. It is recommended that differencing should be done as few times as possible.

Using de-trended series for the calculation of the expected seasonal values in the best performing model may produce better forecasts. Future expected values can also be made to depend on the predicted underlying trend using linear extrapolation. The seasonal adjustment method may be used as a probabilistic risk prediction method by calculating confidence (or prediction)

intervals around the forecast values. This may be done by calculating separately for each lead time the root mean squared errors from a "training" data set. The 95% confidence interval will then range between $F_t - 1.96E_t$ and $F_t + 1.96E_t$, where F_t is the forecast value for time t and E_t is the corresponding root mean squared error.

The best performing seasonal adjustment method may be used in combination with other forecasting methods based on weather variables. It has been shown that forecasts calculated by taking (weighted) averages of values obtained from two or more methods are more accurate that the individual forecasts (Makridakis *et al.* 1998). The seasonal adjustment method may also be readily implemented in areas where other predictor variables are lacking as a rough guide for preparedness. In all cases, it is important to bear in mind the basic implicit assumption of this method that recent deviations from the expected means will continue to be observed in the future months.

How is variation in epidemic risk linked with environmental factors?

A study on the spatial and temporal distribution of epidemic events in Ethiopia indicated that epidemics affected different areas in different years and abnormal increase in meteorological variables (especially minimum temperature) played a major role in triggering epidemics (Chapter 4). Studies are on-going to understand in more detail the association of epidemic-related environmental and entomological factors. The general framework of this association has been proposed to incorporate meteorological, entomological and confirmed morbidity variables as well as a potentially useful proxy for dynamic immunity (Chapter 2).

Close inspection of past morbidity records to identify epidemic years, and then studying what was particular about the weather patterns in the months that preceded the epidemics could provide a basis for monitoring the next occurrence of similar combination of factors that may herald a new epidemic (A. Beljaev, personal communication). Our analysis of recorded epidemics in relation to weather anomalies in preceding months has indicated that abnormal increase in minimum temperature was an important determinant (Chapter 4). In another study carried out in Ethiopia, it was found that minimum temperature was associated with malaria cases in cold districts, whereas in most of the hot districts the association was not significant (Teklehaimanot *et al.* 2004). In the highlands of Rwanda, minimum temperature predicted incidence of cases best at higher altitudes where there was a remarkable increase in malaria (Loevinsohn 1994). In Madagascar, minimum temperature during two months at the start of the malaria transmission season accounted

for most of the variability in incidence between years, suggesting the importance of using data corresponding only to months when the human-vector contact is greatest (Bouma 2003).

The 48 reported epidemic episodes from the different areas in our studies for which data was available between September 1986 and August 1993 were not associated with abnormal rainfall or maximum temperature. However, there is a possibility that abnormally high rainfall could have caused epidemics in arid and warm lowlands. On the other hand, an abnormally high rainfall following the El Niño event of 1997-98 has caused epidemics in the highlands of Uganda (Kilian *et al.* 1999; Lindblade *et al.* 1999). In Ethiopia, it has been reported that rainfall was associated with increase in malaria cases in hot areas at relatively short lags, while a delayed association was observed in cold districts (Teklehaimanot *et al.* 2004). The use of rainfall data for early warning of epidemics, especially in arid areas such as in north-eastern Kenya, is currently feasible through the use of remote sensing data provided through the African Data Dissemination Service of the Famine Early Warning System (Hay *et al.* 2001). We have also observed instances where epidemics of malaria affected some highland areas in southern Ethiopia as a result of a rainfall deficit following a drought condition (unpublished data). In the highlands, rainfall deficit can cause epidemics due to vector breeding in pools formed in river beds.

Is biological reasoning useful in statistical modelling of environmental data for predicting malaria incidence?

Statistical modelling of the effects of factors including weather variables, vector breeding, parasite development and population (communal) immunity based on biological relationships of these variables has provided an important platform for developing further models for prediction of malaria incidence (Chapter 5). We formulated a statistical model on the basis of assumptions that take into account the transmission dynamics of malaria incidence, including the effects of temperature and rainfall on the vectorial capacity and the varying degrees of health facility attendance by patients from areas with differing transmission intensity or communal immunity. This gave rise to a linear mixed model in which the incidence in the previous month entered into the model with area-specific coefficient (random effect) depending on the expected endemicity level. The external predictor variables (rainfall and temperature) were assumed to have fixed effects. The resulting linear mixed model included rainfall 2 and 3 months earlier and temperature in the previous month together with incidence in the previous month. This model explained

most of the variation in incidence and formed the platform on which more detailed models could be developed.

The effects of environmental variables on malaria transmission dynamics are various and complex. Our model included only minimum temperature and rainfall and did not include other variables such as relative humidity. Increased humidity has been reported to have caused epidemics in Venezuela and Argentina (Onori and Grab 1980). It has been shown that variations in relative humidity can have a remarkable impact on the longevity of vectors. Mosquito survival probability has a very significant impact on malaria transmission as the parasite is more likely to complete the sporogonic cycle in long-living vectors. The entomological inoculation rate is indeed extremely sensitive to slight changes in the survival rate and the sporogonic cycle (Onori and Grab 1980). Laboratory studies have indicated that the interaction of temperature and relative humidity affects survival of *A culcifacies* in non-linear fashion. Optimum longevity was observed with temperatures of 25 ^{o}C-30 ^{o}C and relative humidity of 60%-80% under laboratory conditions (Pal 1943). As temperature increases beyond 25 ^{o}C, vector survival declines. While such an increase has a negative impact on survival on one hand, it has, on the other hand, a positive effect on transmission as increased temperature shortens the sporogonic cycle. There is also interaction between temperature, relative humidity and rainfall. Although our model sheds light on the importance of the approach of formulating a statistical model on the basis of biological assumptions, more research is needed to model all the different interactions and effects of environmental factors in detail.

Our model has only partly accounted for the variations in immunological status of populations as the result of transmission intensity. The prerequisite for the occurrence of an epidemic is the existence of a large number of non-immunes who would be clinically ill when infected. Epidemics are unlikely to affect populations living in highly endemic areas, where most people have well-developed immunity; therefore, there is an inverse relationship between endemicity and epidemicity (Nájera *et al.* 1998). Disturbance of a previously existing equilibrium of the ecological system consisting of interacting populations of the parasite, the vector and the human host will give rise to epidemic situations. Our study indicates that the dynamics of immunity should be incorporated in incidence prediction models. This will require further studies to select suitable parameters to measure immunity or its proxy.

How should malaria epidemic prevention and control be linked to epidemic risk assessments and what are the challenges?

The various elements of epidemic risk monitoring need to be associated with available prevention and control options through probabilistic forecasts and related decision systems that take into account resource constraints (Chapter 6). Several issues related to challenges facing health services in epidemic-prone areas in terms of taking effective preventive and control measures have been discussed, including current needs for practical epidemic early warning and dynamic risk mapping models, the constraints posed by parasite resistance to traditionally inexpensive antimalarials, as well as other problems.

Overall, the research outputs of this thesis have led to the recognition of the need to implement effective epidemic management systems. As the direct outcome of this research, at least two countries (Kenya and Uganda) have indicated their keen interest to extend the outputs of the new surveillance system and detection algorithm piloted in four of their districts to other areas at risk.

Risk assessment and early detection of epidemic situations are necessary for any prevention or control measures to have a significant impact in reducing the morbidity and mortality consequences. In the context of decisions that may have important economic impacts, all epidemic response measures should be planned in line with probabilistic warning signals provided by risk monitoring activities. Selectiveness and timeliness of response is of great importance in countries with resource constraints. Our study shows that setting up of strong surveillance systems for early detection of epidemics is technically feasible. This will be useful for taking timely measures to contain outbreaks of limited geographical coverage, but in the case of a widespread regional or nationwide epidemic affecting large areas, a system for early warning at longer lead times will be necessary for comprehensive preparedness. This calls for the need to attach decision making processes to activities such as seasonal climate forecasts or monitoring El Niño conditions, and using suitable models developed on the platforms laid by this research and other studies.

The use of satellite-derived and interpolated rainfall estimates (available through the Internet from the Southern Africa Development Community Drought Monitoring Centre, the Famine Early Warning Systems Network or the International Research Institute for Climate Prediction websites) has been recommended for malaria epidemic early warning (Connor *et al.* 1998; DaSilva *et al.* 2004). Although these provide useful information on a near real time basis, the geographical scale for which the products are available is either too large to take into account local variations in malaria epidemiology or too

sophisticated for use at lower levels of the health service systems, thus making specific prevention and control measures difficult. An early warning of regional epidemics may be recommended using such data at national levels for preparedness, but such warning is not generally useful for taking specific preventive measures according to area-specific needs.

Non-climatic factors should also be considered in developing epidemic early warning systems. Civil unrest and economic crisis in many developing countries are also factors that have contributed to increasing the risk of epidemics (Nájera *et al.* 1998). The increasing trend of malaria in the western highlands of Kenya might have been due to drug resistance of the parasite (Malakooti *et al.* 1998). Even brick-making, an important economic activity in western Kenya, has been linked to increased vector densities (Carlson *et al.* 2004).

Current evidence shows that epidemic forecast and risk mapping is potentially useful for preparedness and prevention but more research is required to fine-tune the available models and to develop robust systems with minimal inputs of variables.

It would be essential to consider a number of factors that would determine the effectiveness of prevention of control measures and the challenges facing developing countries at risk of epidemics (Chapter 6). The most important of the current challenges is the requirement for stocking the significantly expensive ACT drugs for both mass fever treatment and patient management at health facilities, and the need for more developed capacity for selective vector control.

Seasonal preparedness is also an important prerequisite for effective epidemic management. Many mesoendemic areas show seasonality of malaria mainly based on the seasonal patterns of rainfall, temperature and humidity. Experience shows that malaria epidemics in these areas almost always occur superimposed over the seasonal increase during the peak malaria season(s). As a result, it has been recommended that improved planning and preparedness before the seasonal cycles should be given emphasis. Together with national level early warning, this approach provides a feasible strategy for epidemic management in East African highlands (Hay *et al.* 2003). Although there are epidemic outbreaks that have affected some areas during non-malaria seasons (e.g. following drought conditions), it is important to correctly identify the usual start and end of the transmission season for each area for preparedness purposes or, in some cases, for regular preventive measures such as annual indoor residual spraying.

7.2 Challenges of epidemic surveillance

Sentinel surveillance

Sentinel surveillance has the advantage of reducing the workload of health staff (especially those at district levels) in terms of data entry and analysis, and hence increasing efficiency and accuracy in surveillance data management and reporting (Chapter 2). High quality data can be generated from a small, manageable number of health facilities (de Savigny and Binka 2004) and frequent supervisory support can be provided from the district levels.

On the other hand, in a sentinel-based surveillance system, it is assumed that the selected health facilities are representatives of health facilities in the surrounding areas. However, this assumption may not always be met. Usually 'catchment' areas represented by a sentinel site are epidemiologically heterogeneous. The epidemiology of malaria can greatly vary within short distances. This makes it difficult to delineate the geographical extent of an abnormal transmission during epidemic outbreaks, to determine coverage requirements for prevention or control. Furthermore, there may be inherent differences among health facilities. As an example of such differences, government-owned facilities have put in place user fees waiver schemes whereas non-governmental or private facilities often charge patients for services. User fee has been found to be an important determinant of the number of patients seen at health facilities (Yeneneh *et al.* 1993; Miguel *et al.* 1999; Adera 2003). Our experience in East Africa indicates that non-governmental (mission) health facilities in fact see significantly fewer patients compared to governmental ones mainly because of the relatively high fees they charge, and many of them receive more admission (or in-patient) cases rather than outpatient cases.

The new surveillance system relies on data from selected sentinel sites which were considered "representative" of their surrounding areas within a district. The fact that malaria can exhibit high spatial variability within short distances means that extra care must be taken to ensure that sentinel sites are truly representatives of their surrounding area. Unless areas represented by a sentinel surveillance site are fairly homogenous in terms of the epidemiological pattern of malaria, it is often difficult to delineate the geographical extent of an outbreak. To address this problem, it may be useful to rapidly look at morbidity data from neighbouring non-sentinel health facilities, to see if there is similar rate of increase. Alternatively, (spatial) epidemic risk maps such as the one produced for Eastern African countries within the MARA/ARMA Project (www.arma.org.za) (Cox *et al.* 1999) can be a useful guide to determine epidemiological homogeneity, although the low

resolution of these maps makes it difficult to provide practical recommendations regarding the coverage of specific prevention or control measures.

It is therefore essential to pay due attention to selection of sites early in the set of the surveillance system. One way of doing this is to objectively compare the historical morbidity patterns of data collected from several health facilities in the district. The similarity of the baseline patterns may be studied through spatial-temporal cluster analysis. There are a number of techniques available especially for spatial cluster analysis (Elliot *et al.* 2000). These might prove difficult to implement at district levels but there is a possibility of automating at least some of the essential steps, using software specifically designed for such purpose.

Here, we propose a way of comparing malaria morbidity patterns in different health units. This method is based on the principle of clustering by calculating the (Euclidean) "distance" between two time series and then determining their similarity (Ghosh 2003). The Euclidean distance between two n-vectors a and b where $a = (a_1, a_2, ..., a_n)$ and $b = (b_1, b_2, ..., b_n)$ can be defined as:

$$D_{a,b} = \|a - b\| = \left[(a_1 - b_1)^2 + (a_2 - b_2)^2 + ... + (a_n - b_n)^2\right]^{1/2} \qquad (7.1)$$

where a_i and b_i are relative incidence values in month i in health units a and b, respectively, obtained by dividing log-transformed monthly incidence values by their overall mean as discussed in Chapter 3. The relative incidence, rather than the actual incidence values, should be used as the calculation of the distance and similarity between two or more series requires standardizing across the different series.

The similarity $S_{a,b}$ between the two vectors can be then calculated as follows:

$$S_{a,b} = [\exp(-D_{a,b})]^2 \qquad (0 \le S_{a,b} \le 1) \qquad (7.2)$$

We will illustrate this procedure by using an example. Figure 7.1a shows monthly incidence of *P. falciparum* malaria seen at 6 malaria laboratories in north-western Ethiopian highlands during September 1986-August 1989. The relative incidence values with mean of 1 for each site are given in Figure 7.1b.

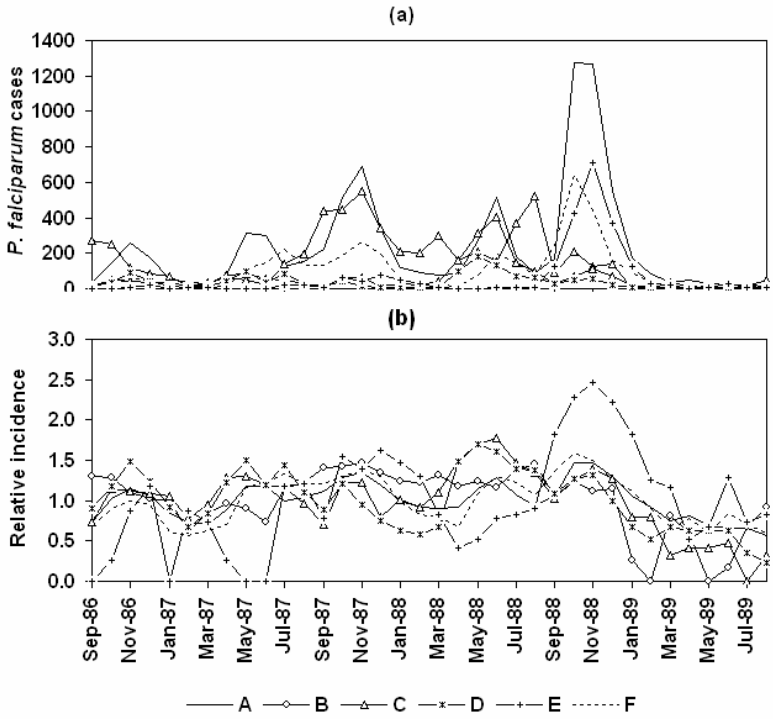

Figure 7.1 Monthly incidence (a) and relative incidence (b) of *P. falciparum* cases seen at 6 sites in north-western Ethiopia, September 1986—August 1989, namely in Bahirdar (A), Koladiba (B), Debretabor (C), Addiszemen (D), Bichena (E), and Finoteselam (F).

The distance and similarity (expressed as a percentage) are given in Figure 7.2. It is clear that Sites A and F have similar pattern, irrespective of the fact that there are on average more than twice the number of cases seen in the former compared to the latter. Sites C and D have also similar pattern. These pairs may be grouped together and represented by one sentinel site (Figures 7.2b, 7.3). Which one of the pairs to choose as a site will depend on other factors such as geographical location. In this particular example, 4 sentinel sites may be formed to monitor morbidity in the area. The obtained similarity figures may also be used in combination with other similarity values calculated from factors such as altitude, actual incidence levels and geographical proximity. Additional research is needed to find proper cut-off points of distance or similarity to test significant differences between sites.

In a different approach, the number of sites that can be managed with the available resources may be determined *a priori* and similarities between two groups or sets may be calculated. This involves a more complicated procedure, especially when the number of health facilities under consideration is high. At the level where classification of health facilities is required based on their similarity, the first decision to be made is the manageable number of sentinel sites that can be handled with the available resources.

Suppose k is the number of sentinel sites for which data collection, entry and analysis can be handled. To classify the health facilities into k groups, it will be necessary to form all possible k sets out of the universal set U, the total number of eligible health facilities. For example, if $U = 3$ and $k = 2$, 3 different pairs of sets of health units can be formed, h_1, h_2, h_3: $\{h_1\}$ and $\{h_2, h_3\}$; $\{h_1, h_2\}$ and $\{h_3\}$; and $\{h_1, h_3\}$ and $\{h_2\}$. Then the (mean) relative incidence values should be calculated for each set as described above and in Chapter 3. The distance and similarity between the sets in each pair can then be calculated. Finally, the groups that are least similar will be selected. Suppose the similarity values are 0.60, 0.35 and 0.05, for the 3 pairs, respectively. The third pair represents sets which are the least similar. The sentinel sites to be selected will then be h_2 and either of h_1 or h_3. The formation of sets will get more complicated as the number of health facilities increases and therefore this classification method may not be practical unless a specifically designed computer program is used to automate the computation process.

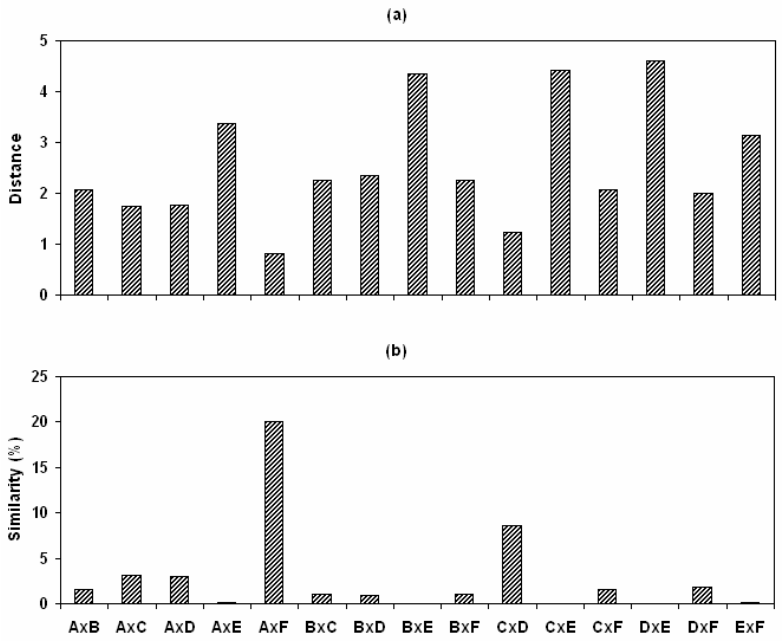

Figure 7.2 Distance (a) and similarity (b) between different combinations of pairs formed from a total of 6 sites in north-western Ethiopia calculated from relative incidence data using equations 7.1 and 7.2, respectively (AxB = distance or similarity between Site A and Site B; see Figure 7.1 for site names).

A potential problem with the method described above is that it does not account for uncertainty in measurements. For example, one health facility may have — on average — the same pattern as another, but due to random variation there may still be a substantial difference. Further investigations are recommended to develop a method for testing the statistical significance of the difference or similarity between two series.

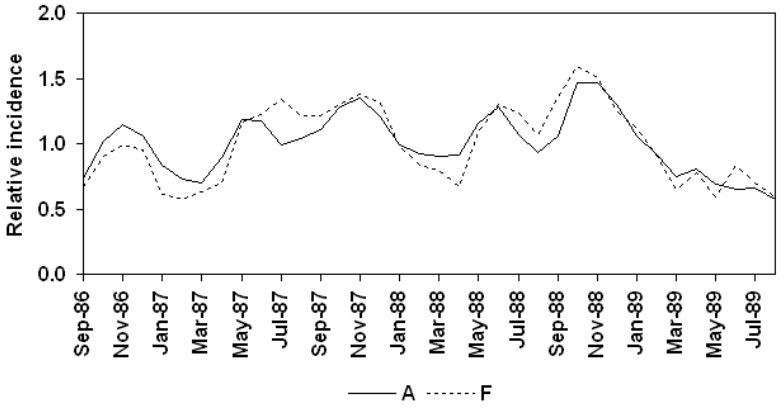

Figure 7.3 Visual similarity of morbidity patterns between Sites A and F (Bahirdar and Finoteselam) as plotted from relative incidence values.

Detection algorithms

The expected duration and severity of an apparently abnormal incidence is usually difficult to predict. Statistically, a normally distributed incidence can exceed the 1 standard deviation threshold due to chance variation 15.9% of the time (Chapter 4). This means that incidence can exceed the threshold by chance at least once, $100 \cdot [1-(1-0.159)^n]\%$ of the time during n successive time points. The probability that $1,2,...,n$ successive incidence values exceed the threshold value by chance is 0.159^n. It follows that the likelihood of observing n "abnormal" values consecutively by chance approaches 0 as n increases. Therefore, occurrence of such a phenomenon will improve the specificity of detecting abnormal incidence. In connection with this, the main issue for the health services is to find a reasonable balance between: (i) waiting too long before deciding whether incidence exceeding a threshold value is the beginning of a true epidemic; and (ii) declaring too quickly a short-lived and/or a "normal" fluctuation exceeding the threshold by chance as an epidemic outbreak. It has been reported that false alarms are possible with some epidemic detection algorithms (Hay *et al.* 2002).

As a general rule, we tentatively propose that all the following criteria should be fulfilled before an increase is declared as an epidemic, based on log-

transformed, de-trended and smoothed series of weekly malaria morbidity data with at least 5 years of baseline: (a) the standardized departure calculated for each week exceeding the value of 1 for 2 consecutive weeks (or incidence exceeding the week-specific mean plus 1 standard deviation threshold); (b) an increasing trend in the standardized departure values during the recent 4 weeks; and (c) incidence exceeding the overall mean plus 1 standard deviation threshold for 2 weeks. A severe epidemic should be expected if these criteria are fulfilled simultaneously at different sentinel sites within a district. Although these criteria may be used as a rough guide, their validity in detecting true epidemics remains to be evaluated. A preliminary result of such evaluation using Monte Carlo simulation using a hypothetical sample of 10,000 years showed that the probability that criteria (a) and (b) occur simultaneously by pure random chance in any particular week is 0.32%. The use of these criteria together with (c) is expected to further reduce the chance of observing any false alarms.

Methods of epidemic detection can vary considerably in terms of their sensitivity and specificity. Performances of different methods of triggering alerts for early detection were evaluated in terms of potentially prevented cases. Theoretical comparisons were made by calculating potentially prevented cases under different scenarios mainly based on lead time to control measures after detection and the expected effectiveness of control measures (Teklehaimanot *et al.* 2004). Simple weekly percentile thresholds performed well for epidemic early detection when tested on data from Ethiopia. Although comparing their performance is difficult, studies have indicated that the simple epidemic detection techniques require significant refinement before they can be considered robust enough for operational use (Hay *et al.* 2002). Most of the previous techniques lack ways of dealing with changing disease patterns or the endemicity equilibrium. The detection algorithm we developed has an in-built capacity to "adjust" the expected weekly number of cases for any given time point based on the trend in the whole baseline data (Chapter 2). All baseline data except data during the recent 3 months are used to determine the expected cases which can change from year to year based on the underlying trend. The performance of this new algorithm still needs to be evaluated in comparison with other methods.

An increase in the parasite rate (or percent positive) among patients seen at health facilities where blood tests are routinely carried out may be a good indication of abnormal transmission. Data on confirmed cases of *P. falciparum* and *P. vivax* from Finoteselam Malaria Laboratory in north-western Ethiopia shows that the parasite rate closely follows the number of positive cases (Figure 7.4a). Traditionally, malaria laboratories attempt to microscopically test all self-presenting patients. A scatter plot of log number

of confirmed cases against the parasite rate indicates a strong linear relationship (Figure 7.4b). The slope of such a relationship will most likely vary between areas, but in the case of Finoteselam, it seems that epidemics are associated with high parasite rates (mostly exceeding 50%). This parameter may be used for epidemic early detection in the absence of more sophisticated techniques or in sites with microscopy, or lacking sufficient baseline data.

This method may also be used in addition to the other epidemic detection algorithms. Nevertheless, in health facilities where only a selected number of patients go through the laboratory confirmation process, the parasite rate may be seriously biased and is therefore not recommended.

Integration of the surveillance system

Many African countries have set up Integrated Disease Surveillance and Response (IDSR) units but most of these have not been effective in recognizing outbreaks at their early stages and/or in taking timely response measures. The IDSR system is a strategy designed to detect and respond to the diseases of epidemic potential, diseases of public health importance and diseases targeted for eradication and elimination. The system is currently being decentralized to the district level.

Current disease surveillance and response systems are geared towards the needs of (highly) endemic areas, if at all they exist or are functional. The need for special systems in epidemic-prone areas both in terms of monitoring disease situations and strategies for response has been either ignored or an attempt has been (wrongly) made to adapt/modify systems suitable only in endemic areas. The main challenge is integrating surveillance of the target diseases, as many of these differ in terms of the extent of detailed data requirements, coverage, frequency of reporting and type of response needed. For example, malaria epidemic surveillance is needed most in the districts at risk of malaria outbreaks. The most important step that ministries of health may need to take in order to meet this challenge is to set up ways of coordinating design and use of practical surveillance systems and tools for data collection by bringing together all concerned units and levels in the health services. Currently, there is a serious lack of coordination between units responsible for health and management information systems and surveillance of epidemic diseases in most countries. This leads to duplication of efforts and ambiguities of responsibilities. There is a need to coordinate the various activities of the different units regarding malaria epidemic surveillance.

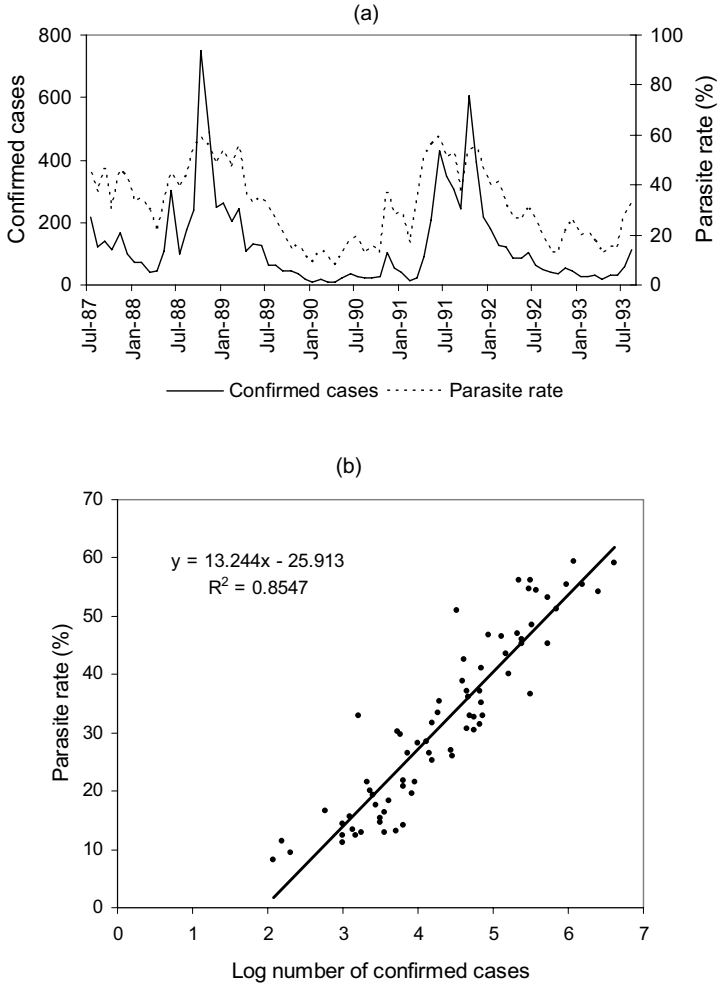

Figure 7.4 (a) Confirmed malaria cases and the associated parasite rates at Finoteselam Malaria Laboratory, north-western Ethiopia, July 1987-August 1993; (b) The parasite rate from the same data set as a function of the (log) number of confirmed cases, indicating a linear relationship.

7.3 Highland malaria and climate change

The effect of climate change on trends in malaria transmission in the highlands still remains controversial. In recent years, a number of published works have looked at trends in temperature and malaria especially in the East African highlands. Some studies have claimed that disease incidence is increasing in the absence of any apparent trends in temperature in these areas over the last few decades, attributing the phenomenon to non-climatic changes such as increased drug resistance (Hay *et al.* 2002; Shanks *et al.* 2002). However, studies have shown the existence of a significant trend in temperature data from the same areas (Pascual *et al.* 2006). The effect of climate on epidemics of malaria is most important in highlands and arid areas where temperature and rainfall are limiting factors for transmission. In recent years, there has been a general upward trend of malaria incidence in highland areas, some of which were previously considered malaria-free. However, the slope of this trend greatly varies between areas.

Data from Ethiopia indicate that some highlands have attained a higher equilibrium level whereas very little trend is noticeable in others. Figure 7.5 illustrates this point using two urban centres: Abomsa in the eastern escarpment of the Rift Valley and Bahir Dar in north-western Ethiopia. Both areas are located at similar altitudes of about 1,800 metres, but possess different topographic and climatic characteristics, rates of economic development and population movement patterns. Abomsa is a small rural town with a population of 12,800 (1999 estimates), whereas Bahir Dar is a larger urban centre with rapid development both in terms of economic/commercial activities and population size since it became the capital of the Amhara Regional State in the early 1990s; its population was estimated at 112,000 in 1999. Owing to its flat topography, Bahir Dar is often affected by floods. The two urban centres also significantly differ in their average annual rainfall: 1,466 mm for Bahir Dar and 960 mm for Abomsa. It is clear that after the mid-1990s, malaria incidence in Bahir Dar has dramatically increased and it now appears that a new equilibrium level has been established. Abomsa, on the other hand, is affected from time to time with abnormal increase but there is little change in the overall trend.

Although drug resistance by *P. falciparum* may have contributed to the upward trend in malaria in the highlands, the difference in trends observed between the two sites is unlikely to have been due to chloroquine resistance, which was uniformly high in most areas in Ethiopia during the 1990s (unpublished data). It seems that difference in demographic changes and population movement patterns between the two sites, coupled with greater

potential for malaria transmission due to its flat topography and risk of flooding may have probably given rise to the observed difference in trends.

In a study carried out in Rwanda, it was found that minimum temperature predicted malaria incidence best in higher altitude areas which experienced the most increases during the 1980s (Loevinsohn 1994). Abnormal increase in minimum temperature has also been shown to precede epidemic events in the Ethiopian highlands in the late 1980s and early 1990s (Chapter 4). A study carried out using data from 7 highland sites in East Africa has concluded that climate variability, rather than long-term changes in mean temperature, plays an important role in initiating malaria epidemics in the East African highlands (Zhou *et al.* 2004; Zhou *et al.* 2005) although the method used to test this hypothesis has been challenged (Hay *et al.* 2005).

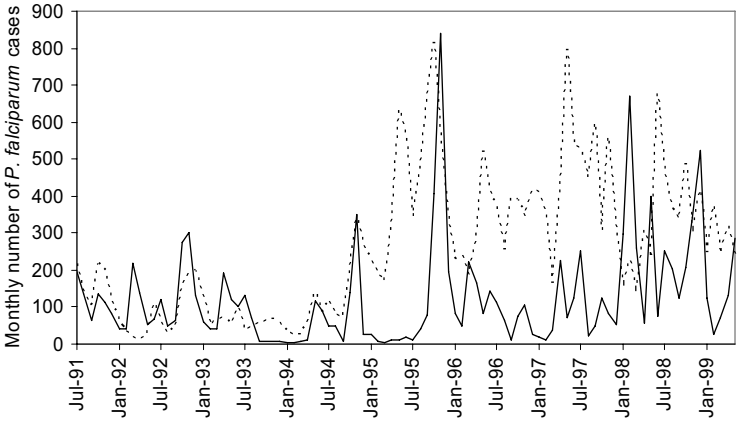

Figure 7.5 Incidence of *P. falciparum* cases reported from Abomsa (solid line) and Bahir Dar (broken line) in Ethiopia.

Nevertheless, studies have continued to confirm the association of epidemic malaria with El Niño events in many parts of the world. As an example, in Columbia, researchers have analyzed malaria data for the period 1980-1997 to present evidence that the El Niño phenomenon intensifies the annual seasonal malaria transmission cycle (Poveda *et al.* 2001). Several reports have already produced consistent findings regarding the association

between El Niño and malaria in the coastal regions of Venezuela and Columbia (Kovats *et al.* 2003).

Although there is still much uncertainty about the role of climate change in determining long-term trends in incidence in the highlands, a combination of multiple factors are probably responsible, including climatic as well as non-climatic causes such as population movement and changes in the demographic characteristics, reduced intensity and quality of malaria control measures (in particular vector control) and drug resistance of the parasite. Nevertheless, current evidence appears to show that climate variability plays an important role in causing short-term, but at times widespread, epidemics in these areas.

7.4 Dynamics of communal immunity

In the study of the use of weather variables in malaria epidemic modelling, we concluded that inclusion of dynamic immunity would be necessary (Chapter 5). The study of immunity at the population level requires longitudinal serological surveys (Molineaux and Gramiccia 1980; John *et al.* 2005; Munyekenye *et al.* 2005). In the absence of serological data, adult-to-child ratios of hospital admissions have been used in the highlands of Kenya to study transmission intensity (Hay *et al.* 2002). Areas with intense transmission are characterised by absence of severe disease in adults and older children as a result of effective immunity to malaria, whereas in areas with less intense transmission all age groups can be affected. This difference can be reflected in the age structure of malaria patients seen at health facilities — as relatively more children are expected among cases in areas with higher communal immunity levels.

Here we will use proportion of children under 10 years of age among all confirmed malaria cases reported from several areas across Ethiopia to study the relationship with intensity of transmission. We used data from malaria detection and treatment posts in Ethiopia from September 1987 to August 1988 (data relating to age groups was available only for total confirmed cases and not separately for each *Plasmodium* species; average age of morbidity cases could also be used for such analysis if patient-specific data is available). We also used the data to study the existence of seasonal variations in the proportion of children and the possible association of such variations with the magnitude of the proportion. The most important implication of this study is to show the potential of using the proportion of children among patients seen at health facilities as a proxy measure for dynamic immunity, which may be incorporated in prediction models that are based on data generated from health facilities.

The results of the analysis showed that there is a clear spatial variation in the proportion of children under 10 years old among confirmed cases of malaria seen at health facilities. The proportion increased with increasing incidence levels, indicating that relatively more children visit health facilities as transmission increases, given about equal size of catchment areas (Figure 7.6).

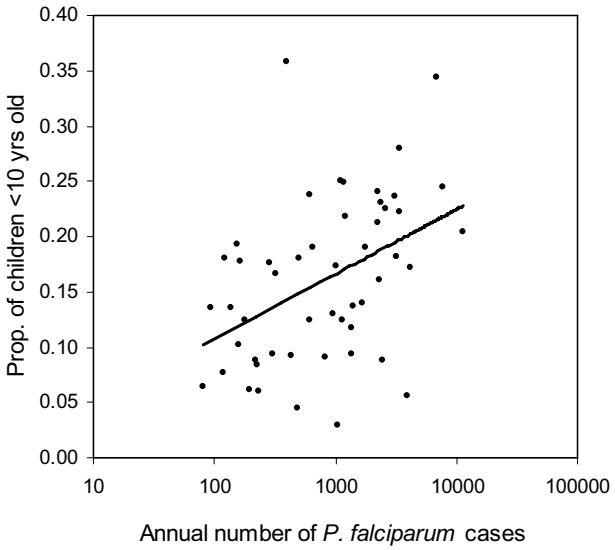

Figure 7.6 The proportion of children under 10 years of age positive for malaria as a function of annual number of *P. falciparum* cases in each site. Each dot represents one site. There are no huge differences between sites in terms of population size and number of malaria laboratory diagnosis and treatment facilities so the number of cases indicates real differences in malaria morbidity levels. As the age group data did not distinguish between the different *Plasmodium* species, the numbers of *P. falciparum* cases by age group were estimated from the proportions of this species out of the total confirmed.

The proportion of children under 10 years among patients also varied with number of *P. falciparum* cases seen each month (Figure 7.7). These results show that the use of this proportion as a proxy for dynamic immunity

in prediction models should take into account the underlying incidence levels as the strength of the association is area-specific. This indicates that a correction factor may be required in such models. More detailed studies are required to ascertain the potential use of the age-specific incidence at health facilities as a proxy for dynamic immunity, through concurrent longitudinal serological studies. It is worth noting that an erratic pattern might result in areas with low number of cases (e.g. as in Alaba in Figure 7.7, where the number of cases seen before June 1988 was too low to adequately determine the proportion of children). Furthermore, we expect significant changes in population immunity levels to occur only after huge outbreaks affecting a large part of the population, or following a long period without any outbreaks. On the other hand, in areas with high endemicity (such as Gambela in western Ethiopia as in Figure 7.7), there was no apparent seasonal change in the proportion of children throughout the year. Therefore, this phenomenon is better studied over longer periods and in areas with low transmission but where morbidity is sufficiently high for the calculation of accurate proportions. In situations where patient-specific data are available, temporal changes in the average age of cases at health facilities may also be studied.

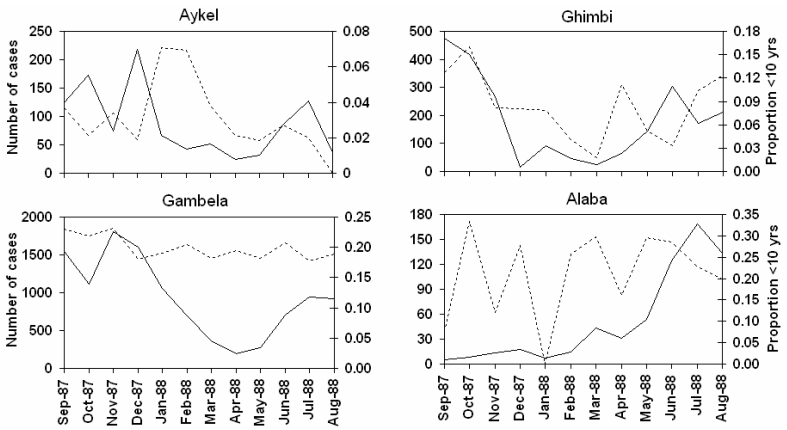

Figure 7.7 Seasonality of *P. falciparum* malaria (solid lines) and the proportion of children under 10 years among confirmed cases (broken lines). The graphs represent four examples of the patterns observed, namely, proportion of children: lagging behind confirmed cases (Aykel), trailing number of cases (Ghimbi), showing no obvious seasonality (Gambela), and showing irregular pattern (Alaba).

7.5 Conclusions and recommendations

Conclusions

- A method using seasonal adjustment provides better forecasts of malaria incidence in epidemic-prone areas than other proposed methods, including ARIMA. This method can be used with a minimal resource requirement of a three-year baseline of monthly morbidity data.
- A new epidemic detection algorithm, involving continuous removal of baseline trends and using a combination of two threshold limits, has been successfully implemented in epidemic-prone districts, within a sentinel surveillance system with an automated, weekly data analysis at district levels.
- Unusually high minimum temperature in preceding months is a useful indicator of impending malaria epidemic in highlands.
- A biologically motivated statistical model including malaria incidence and minimum temperature in the previous month and rainfall 2 and 3 months earlier explained most of the variance in data obtained from Ethiopia.
- Malaria early warning, early detection, preparedness and response are integral parts of an effective epidemic management system. Current challenges in implementing such a system include developing local capacity for dynamic risk mapping, rapid response and selective and timely vector control.

Recommendations

- The sentinel surveillance system and automated epidemic detection algorithm tested in pilot districts in East Africa is a useful epidemic monitoring approach and should be implemented in all epidemic-prone areas.
- There is a need for new methods to account for dynamic communal immunity in models for predicting malaria epidemics.

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Summary

At least one million people are killed by malaria every year and 80% of the deaths occur in Africa south of the Sahara. Most of the populations in areas with high intensity of transmission develop immunity to the severe forms of the disease relatively early during childhood—thus adults are usually at a relatively low risk of mortality. Malaria transmission is mostly stable in these areas with little fluctuation in incidence of disease. In contrast, the transmission intensity is normally low in highlands and arid lowlands. Most of the human populations in these areas possess little or no immunity to the disease. As the result, all age groups are affected during malaria outbreaks, leading to high mortality rates.

Epidemic malaria—defined as an acute exacerbation of disease out of proportion to the normal to which the community is subject—continues to affect several regions in Africa, the Americas, Asia, and some parts of the Middle East. Most of the affected areas include highlands or highland fringes where transmission is mostly determined by temperature, and arid or semi-arid areas where availability of surface water plays a major role. It has been estimated that malaria epidemics can cause, every year on average, up to 12 million malaria episodes and 155,000—310,000 deaths, which is equivalent to 12-25% of the annual worldwide malaria deaths.

Various combinations of factors lead to epidemics. These include: anomalous weather conditions, increasing drug resistance by the parasite, failure or deteriorating vector control activities, and high population movement between areas of varying endemicity due to seasonal labour or civil unrest. Malaria epidemic early warning is based on monitoring transmission risk indicators for the prediction of the timing of an increase (such as abnormal rainfall and/or temperature), and population vulnerability indicators for the prediction of the severity of impact (such as loss of immunity due to recent history of low transmission). Prediction of malaria epidemics using such factors can give lead-times of weeks to months, during which appearance of anomalies in disease incidence can be closely monitored and preventive and control measures targeting specific areas planned and implemented.

Investigating the various effects of environmental variables to understand the triggering mechanisms of epidemic malaria is useful to develop prediction systems for prevention and preparedness. Temperature is known to affect the length of sporogony—the development cycle of the *Plasmodium* parasite within the mosquito vector. The warmer the environmental temperature, the shorter the sporogonic cycle—a favourable condition for the accelerated transmission of the parasite during the life span of the vector. Warmer temperatures also lead to an accelerated growth of the aquatic stages of

mosquitoes. Rainfall deficit in the highlands may result in increased proliferation of vectors by creating breeding grounds in small pools formed as rivers and streams tend to dry. Change in relative humidity affects transmission through its effect on longevity of vectors. On the other hand, excessive rainfall in warm, arid areas can lead to increased transmission due to creation of vector breeding sites and/or decreased temperatures which are normally high and would be lethal both to the vector and the parasite.

In this thesis, we showed the associations of abnormal weather conditions with some documented epidemics of malaria and developed tools that are potentially useful for early warning and early detection. The main emphasis of the thesis was to present efforts to understand malaria epidemic precipitating factors, to develop biologically motivated statistical modelling techniques that make use of these factors for the development of early warning models, to assess the accuracy of simple versus advanced time series methods for incidence forecasting, and to develop and test the technical feasibility of a new epidemic detection algorithm and a sentinel surveillance system in selected highland districts in East Africa. We also discuss how epidemic monitoring systems can be linked to effective response and the associated challenges facing control programmes.

Methods and systems for detecting epidemics at their early phases will be useful to initiate timely control interventions. In **Chapter 2** we discuss a new epidemic detection system which involves recognizing the start of an abnormal situation by measuring changes in local disease incidence in relation to normally expected values. Although this surveillance mechanism offers little lead-time for implementation of preventive measures, it can lead to a rapid response to reduce peak morbidity and mortality. Under the Highland Malaria Project (HIMAL), we successfully set up a new epidemic detection system in four pilot districts of Kenya and Uganda. This system involves a network of selected sentinel health facilities that report to their respective district health offices on a weekly basis, followed by an automated analysis of the data at the district levels and dissemination of the outputs to the different levels of the health services and partners. A new epidemic detection algorithm was developed to assess weekly incidence anomalies taking into account normal variations and underlying trends in the baseline data.

In **Chapter 3** we tested the accuracy of different univariate time series methods for epidemic prediction using only historical morbidity patterns. Five methods were compared using malaria incidence data reported from health facilities in epidemic-prone areas of Ethiopia. A seasonal adjustment method in which forecasts were produced by using month-specific mean (expected) number of cases and deviations of cases in the previous three months from expected values produced the most accurate predictions compared to other

methods, including the statistically more advanced autoregressive, integrated moving average (ARIMA) technique.

We studied the temporal and spatial patterns of climatic variables related to documented malaria epidemics in **Chapter 4**, in order to identify factors that could be monitored and used for prediction. Using data from several sites in Ethiopia, we showed that specific areas were at risk during some years while others temporarily remained risk-free but were affected during other years. Wet highland areas were affected by a widespread malaria epidemic in 1988, whereas fringe areas in the Rift Valley and its escarpments, which had relatively normal transmission in 1988, were affected in 1991 and 1992. Studies of weather patterns indicated that abnormally high minimum temperatures preceded epidemic onsets, but no significant associations were found between above normal rainfall or maximum temperatures and occurrence of epidemics.

Following these observations, in **Chapter 5** we developed a statistical model based on the theoretically expected links between transmission parameters such as the vectorial capacity as a function of minimum temperature and rainfall, immunity levels in populations as a function of the overall incidence levels, and previous values of malaria incidence. This model was fitted using meteorological and morbidity data from 35 sites in Ethiopia, while taking into account spatial and temporal autocorrelations. The model which included rainfall 2 and 3 months earlier, and minimum temperature and case incidence during the previous month explained more than 85% of the total variance in areas with relatively high or low incidence and 55%-85% of the total variance in areas with moderate incidence. The study indicated that a dynamic immunity mechanism should be included in a prediction model. Further studies are required to understand the interactions of the various meteorological, morbidity and immunity variables and how these can trigger epidemics. Collection of detailed longitudinal data on many of these factors is on-going and the data will be used to fine tune models developed so far and to test dynamic epidemic risk mapping methods.

In **Chapter 6** we discuss the malaria prevention and control challenges facing epidemic-prone areas. The main challenge in taking prevention measures before the onset of epidemics is the need to link economic evaluation of expensive measures such as indoor residual spraying of insecticides with area-specific risk with acceptable degree of accuracy. A prerequisite in taking such measures also involves building the capacity of countries for more organized vector control operations. Selective action such as barrier spraying is recommended and should target areas only in close proximity to vector breeding sources. Seasonal preparedness, in particular by stocking sufficient antimalarials, should be an essential part of epidemic

management. Epidemic response should focus on providing effective and rapid treatment for most fever cases. Current challenges include the high cost of effective drugs and developing effective systems for dynamic risk mapping.

We also present some additional results relevant to epidemic prediction and early detection and integrate the findings of the previous chapters in **Chapter 7**. In Section 7.1, we provide answers to the research questions posed in the General Introduction as the result of key findings discussed in the various chapters of the thesis. In Section 7.2, we propose a method for studying the similarities between patterns of historical morbidity data from different health units in north western Ethiopia which can potentially be used in the objective selection of sentinel surveillance sites. In Section 7.3 we discuss the controversial increasing trend of highland malaria and climate change. In Section 7.4, we investigate the potential use of the proportion of younger age groups among patients presenting at health units as a proxy measurement of changing population immunity levels, for inclusion in morbidity-based prediction models. In the final section, we provide conclusions and recommendations based on the findings of the studies.

In conclusion, malaria epidemic prediction, early detection, preparedness and response are integral parts of an effective epidemic management system. Our studies have demonstrated that early detection and prediction of malaria epidemics is feasible, but more research is required to fully understand the processes that trigger epidemics, especially in the highlands. Detailed field investigations and modelling of the various effects of different meteorological factors and their complex interactions as well as the effects of dynamic changes in population immunity levels are required to further improve the prediction and risk assessment systems currently available.

Samenvatting

Per jaar sterven minstens een miljoen mensen aan malaria, en 80% van de sterfgevallen vindt plaats in Afrika, ten zuiden van de Sahara. In gebieden met veel transmissie ontwikkelen kinderen meestal al op jonge leeftijd immuniteit tegen de ernstigste vormen van de ziekte. Hierdoor hebben volwassenen een relatief laag sterfterisico. De malaria transmissie in deze gebieden is vrij stabiel met kleine schommelingen in het aantal ziektegevallen (de incidentie). In hooglanden en woestijnachtige laaglanden daarentegen is de intensiteit van transmissie meestal laag, zodat men daar weinig of geen immuniteit heeft tegen de ziekte. Als gevolg hiervan worden alle leeftijdsgroepen getroffen bij een malaria-epidemie, wat gepaard gaat met een hoge sterfte.

Epidemische malaria—gedefinieerd als een plotselinge verheviging van het aantal malariagevallen ten opzichte van de normale situatie in een gebied—is een bekend probleem in verscheidene delen van Afrika, Amerika, Azië en sommige delen van het Midden Oosten. De meeste gebieden met epidemische malaria bevinden zich op (de randen van) hooglanden waar de transmissie erg afhankelijk is van temperatuur, of zijn droge streken waar de beschikbaarheid van oppervlaktewater een belangrijke rol speelt. Schattingen laten zien dat gemiddeld 12 miljoen mensen per jaar malaria krijgen als gevolg van epidemieën. Hiervan overlijden 155.000—310.000 mensen, d.w.z. 12-25% van de jaarlijkse malariasterfte in de wereld.

Factoren die kunnen leiden tot epidemieën zijn abnormale weersomstandigheden, toenemende resistentie bij de parasiet tegen geneesmiddelen, niet functionerende of kwalitatief slechte vectorbestrijding (= muggenbestrijding; we gebruiken de termen mug en vector door elkaar), en een hoge migratie vanwege seizoensarbeid of politieke onrust. Bij de vroege opsporing van malaria-epidemieën worden transmissierisico-indicatoren (zoals abnormale regenval en/of temperatuur) bijgehouden voor het voorspellen van het moment van een toename van transmissie, en kwetsbaarheids-indicatoren (zoals immuniteitsverlies na een periode van lage transmissie) voor het voorspellen van de ernst van de epidemie. Het zou mooi zijn als het voorspellen van malaria-epidemieën op basis van zulke indicatoren weken tot maanden van tevoren zou kunnen worden gedaan, zodat men gedurende die periode de toename in het aantal malariagevallen nauwkeurig bij kan houden, en maatregelen kan nemen ter preventie en bestrijding.

Onderzoek naar het belang van omgevingsfactoren voor de uitbraak van malaria-epidemieën is van nut voor de ontwikkeling van waarschuwingssystemen waarmee de epidemieën voorkomen kunnen worden, of waarmee men zich althans goed kan voorbereiden op een epidemie. Het is bekend dat de temperatuur invloed heeft op de lengte van sporogonie—dat is

de ontwikkelingscyclus van de malariaparasiet *Plasmodium* in de mug. Hoe hoger de omgevingstemperatuur, hoe korter de sporogoniecyclus—wat zorgt voor een snelle transmissie van de parasiet tijdens het leven van de mug. Hogere temperaturen leiden ook tot een versnelde groei van de stadia van de muggen in het water. Te weinig regenval in hooglanden kan resulteren in een wildgroei van muggen door broedplaatsen in poeltjes die ontstaan als rivieren en stromen opdrogen. Verandering van de relatieve luchtvochtigheid kan de transmissie beïnvloeden door het effect op de levensduur van de vector. In warme woestijnachtige gebieden kan overvloedige regenval juist leiden tot een verhoogde transmissie door het ontstaan van broedplaatsen van de mug of door lagere temperaturen dan de gebruikelijke hele hoge temperaturen die dodelijk zijn voor zowel de vector als de parasiet.

In dit proefschrift tonen we de samenhang aan tussen abnormale weersomstandigheden en gedocumenteerde malaria-epidemieën en we ontwikkelen een methode die gebruikt kan worden voor vroege opsporing van epidemieën. Het proefschrift richt zich vooral op: (1) onderzoek om factoren die malaria-epidemieën bevorderen te begrijpen, (2) het ontwikkelen van een biologisch plausibele statistische modelleertechniek die deze factoren gebruikt voor de ontwikkeling van modellen voor vroege opsporing van epidemieën, (3) het vergelijken van eenvoudige en meer geavanceerde tijdreeksmodellen voor het voorspellen van malaria incidentie, en (4) het ontwikkelen en testen van een nieuw algoritme en een waarschuwingssysteem om epidemieën in geselecteerde hooglanddistricten in Oost Afrika te detecteren. Ook bediscussiëren we hoe systemen om epidemieën te monitoren benut kunnen worden en wat daaruit voortvloeiende uitdagingen voor bestrijdingsprogramma's zijn.

Methoden en systemen voor het vroeg detecteren van epidemieën zijn van belang om tijdig met bestrijding te starten. In **Hoofdstuk 2** bespreken we een nieuw detectiesysteem dat het begin van een abnormale situatie kan herkennen door het meten van veranderingen in de plaatselijke incidentie van malaria. Hoewel dit systeem maar korte tijd biedt om preventieve maatregelen te nemen kan het van nut zijn om de piek van ziekte en sterfte te verminderen. Binnen het 'Highland Malaria Project' (HIMAL) hebben we met succes een nieuwe epidemie-detectiesysteem met succes opgezet in vier testdistricten in Kenia en Oeganda. Het systeem betreft een netwerk van geselecteerde gezondheidsposten (zgn. 'sentinel sites') die wekelijks het aantal nieuwe malariagevallen rapporteren naar hun respectievelijke gezondheidsbureaus, gevolgd door een geautomatiseerde analyse van de gegevens op districtsniveau en verspreiding van de resultaten naar de verschillende niveaus van het gezondheidssysteem. Verder is er een nieuw epidemie-detectie algoritme ontwikkeld om afwijkingen van de wekelijkse incidentie vast te

stellen, waarbij rekening gehouden wordt met normaal verdeelde variatie en een trend over de tijd.

In **Hoofdstuk 3** testen we de nauwkeurigheid van verschillende univariate tijdreeksmodellen voor het voorspellen van epidemieën op basis van historische ziektepatronen. Vijf methoden worden vergeleken, waarbij we gebruik maken van malaria incidentie gegevens zoals gerapporteerd door gezondheidszorgvoorzieningen in gebieden van Ethiopië met een hoog risico op epidemieën. Een 'seasonal adjustment' methode die voorspellingen doet op grond van gemiddelde (verwachte) aantallen malaria gevallen per maand en afwijkingen van die aantallen gedurende de voorgaande drie maanden, gaf nauwkeuriger voorspellingen dan andere methoden, waaronder de statistisch meer geavanceerde 'autoregressive integrated moving average' (ARIMA) methode.

In **Hoofdstuk** 4 bestuderen we de patronen van klimaatvariabelen in relatie tot gedocumenteerde epidemieën, in de hoop factoren te identificeren die kunnen worden gebruikt voor monitoring en het maken van predicties. Op grond van gegevens uit verschillende locaties in Ethiopië laten we zien dat sommige locaties risico liepen op epidemieën in bepaalde jaren, terwijl andere gebieden dan risicovrij bleven, maar getroffen werden tijdens andere jaren. De natte hooglandgebieden werden getroffen door een uitgebreide malaria-epidemie in 1988, terwijl randgebieden in de Rift Valley en zijn steile rotswanden, die een relatief normale transmissie hadden in 1988, juist werden getroffen in 1991 en 1992. Studies van weerspatronen lieten zien dat ongebruikelijk hoge temperaturen soms voorafgingen aan de epidemieën, maar er werd geen significante associatie gevonden tussen hogere dan normale regenval of maximum temperatuur en het optreden van epidemieën.

In **Hoofdstuk 5** wordt een statistisch model ontwikkeld dat gebaseerd is op theoretisch afgeleide samenhangen tussen transmissieparameters. Bijvoorbeeld de 'vectorial capacity' (= gemiddeld aantal secundaire malariagevallen verbreid door muggen per dag per primair geval) als een functie van minimum temperatuur en regenval, en het immuniteitsniveau in populaties wordt gemodelleerd als een functie van het gemiddelde incidentieniveau en van de malaria incidentie in de reeks eraan voorafgaande jaren. Het model is gefit tegen meteorologische en morbiditeitsgegevens uit 35 locaties in Ethiopië, daarbij rekening houdend met ruimtelijke en temporele autocorrelaties. Het model dat gebruik maakte van de regenval 2 en 3 maanden eerder en de minimum temperatuur en incidentie van de voorgaande maand verklaart meer dan 85% van de variantie in gebieden met een relatief hoge of lage incidentie, en 55%-85% in gebieden met een gematigde incidentie. De studie liet verder zien dat een dynamisch immuniteitsmechanisme zou moeten worden opgenomen om tot een goed

predictiemodel te komen. Aanvullend onderzoek is nodig om te begrijpen hoe de verschillende meteorologische-, ziekte- en immuniteitsfactoren samenhangen en hoe deze tezamen epidemieën kunnen veroorzaken. Longitudinale metingen van vele van deze factoren worden momenteel verzameld, en deze gegevens kunnen worden gebruikt om de huidige modellen te verfijnen, en om dynamische methoden voor het in kaart brengen van epidemierisico te testen.

In **Hoofdstuk 6** worden de uitdagingen voor malariapreventie en –bestrijding in gebieden met risico op malaria-epidemieën besproken. Van groot belang is het om economische implicaties van dure preventiemaatregelen, zoals het gebruik van insecticiden, op een voldoende nauwkeurige wijze te koppelen aan het risico op een epidemie. Dit soort maatregelen zijn alleen mogelijk als de betreffende landen goed georganiseerde vector bestrijdingscapaciteit hebben opgebouwd. Selectieve acties zoals 'barrier spraying' zijn belangrijk, maar moeten alleen worden uitgevoerd in de omgeving van broedgebieden van de vector. Een seizoensafhankelijke voorraad antimalariamiddelen is ook essentieel bij het omgaan met epidemieën. Immers, om de gezondheidsgevolgen van de epidemie te beperken, is een effectieve en snelle behandeling van de grote meerderheid van de koortsgevallen een eerste vereiste. Problemen op dit moment zijn de hoge kosten van effectieve geneesmiddelen en de afwezigheid van effectieve systemen voor het in kaart brengen van risico's.

Hoofdstuk 7 integreert de bevindingen van de voorgaande hoofdstukken, en geeft ook nog enkele aanvullende resultaten. In Sectie 7.1 worden de antwoorden op de onderzoeksvragen geformuleerd. De belangrijkste bevindingen uit de verschillende hoofdstukken worden opgesomd. In Sectie 7.2 stellen we een methode voor om de overeenkomsten te bestuderen in patronen van historische ziektegegevens tussen verschillende gezondheidsposten in Noordwest Ethiopië. Deze methode biedt mogelijkheden voor een objectieve selectie van 'sentinel sites'. In Sectie 7.3 bespreken we de controversiële associatie tussen de toenemende trend van malaria in hooglanden en klimaatsverandering. In Sectie 7.4 bespreken we het gebruik van de proportie van malariagevallen op jonge leeftijd als een indicator voor het immuniteitsniveau in de bevolking, zodat de fluctuatie in deze proportie gebruikt zou kunnen worden in verbeterde predictiemodellen.

Concluderend kunnen we stellen dat een effectief managementsysteem de fasen van voorspellen van de epidemie, de vroege opsporing ervan, het voorbereiden op de uitbraak van de epidemie en de feitelijke respons alle vier goed moet dekken. Onze studies hebben laten zien dat vroege opsporing en predictie van epidemieën inderdaad mogelijk is. Verdere gedetailleerde veldstudies en modellering van de effecten van meteorologische factoren en

hun complexe interactie, zijn nodig om, samen met effecten van populatie-immuniteit, de systemen voor predictie en inschatting van risico's verder te verbeteren.

Curriculum Vitae

Tarekegn Abose Abeku was born on 10 August 1964 at Ghimbi (Wollega), Ethiopia. After completing his high school education at Ghimbi Comprehensive Secondary School, he joined the Science Faculty of Addis Ababa University in 1982 and graduated with a BSc degree in Biology in 1986. He studied Mosquito Cytogenetics at the Istituto di Parassitologia, Universita di Roma, Italy, in 1990, and Medical Entomology at the London School of Hygiene and Tropical Medicine, United Kingdom, and graduated with an MSc degree in 1992, winning the James Busvine Memorial Medal and Prize. In 1999, he enrolled in the Netherlands Institute of Health Sciences programme and graduated in 2001 with a DSc degree in Epidemiology from Erasmus University Rotterdam, The Netherlands. He carried out his PhD research on malaria epidemics under the supervision of Prof.dr. J.D.F. Habbema and Dr Sake de Vlas at the Department of Public Health, Erasmus MC, University Medical Center Rotterdam. From 2004 – 2006, he has studied advanced courses in university teaching at the Institute of Education, University of London, within the Professional Accreditation of Teaching in Higher Education (PATHE) Programme.

He started his career in malaria control in 1986 after he joined the National Organization for the Control of Malaria and other Vector-borne Diseases, Ministry of Health, Ethiopia. He served in various positions until 1999, including, as Junior Biologist, Schistosomiasis Section (1986-87), Biologist and later Chief, Medical Entomology Section (1987-93), Head, Vector Biology and Control Service (1993-95), and, Head, Malaria and Other Vector-borne Diseases Control Programme (1995-1999). He has directed and taught national and international malaria courses organized by the World Health Organization for African control programme officers, and has developed a training module for malaria entomology and vector control. He has trained hundreds of malaria control personnel in Ethiopia in malaria entomology, vector control and epidemiology. He has worked for WHO and the Roll Back Malaria as a consultant/temporary advisor in Ethiopia, Kenya, Malawi and Tanzania.

Since 2002, he has been working at the London School of Hygiene and Tropical Medicine as a Research Fellow and later Lecturer where he has been teaching in a number of postgraduate courses, including the Control and Epidemiology of Malaria, Prediction of Disease by Space and Time, and Designing Disease Control Programmes in Developing Countries. His main research interests include malaria epidemic surveillance, modelling malaria transmission in relation to epidemic prediction, operational research on the biology and control of malaria vectors, and epidemiology and control of

malaria in epidemic-prone areas. Apart from his teaching and research activities, his duties at the LSHTM included setting up a malaria epidemic surveillance system in the highlands of Kenya and Uganda as part of the Highland Malaria Project (HIMAL) funded by the Bill and Melinda Gates Foundation through the Gates Malaria Partnership.

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