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Malaria epidemic early warning and detection in African highlands

Tarekegn A. Abeku^{1,7}, Simon I. Hay^{2,3}, Samuel Ochola⁴, Peter Langi⁵, Brian Beard⁶, Sake J. de Vlas⁷ and Jonathan Cox¹

¹Disease Control and Vector Biology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

²TALA Research Group, Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK

³KEMRI Wellcome Trust Collaborative Programme, PO Box 43640, 00100 Nairobi, Kenya

⁴Division of Malaria Control, Ministry of Health, PO Box 20750, Nairobi, Kenya

⁵National Malaria Control Programme, Ministry of Health, PO Box 7272, Kampala, Uganda

⁶Gates Malaria Partnership, London School of Hygiene and Tropical Medicine, 50 Bedford Square, London, WC1B 3DP, UK

⁷Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 1738, 3000 DR, Rotterdam, The Netherlands

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

Corresponding author: Jonathan Cox (jonathan.cox@lshtm.ac.uk).

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well as disease surveillance for effective early warning is being investigated.

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 [1–3; <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’ [4]. 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 [5]. In the past decade, epidemics have been reported from several areas including Ethiopia, Kenya, Uganda, Zimbabwe, Botswana, Mozambique, Madagascar, Swaziland and South Africa [6–14]. 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 [15–17]. Reasonably accurate warning signals could help health services to take targeted and specific preventive measures before the onset of epidemics.

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 [3,16,18,19] (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 [19–21].

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) [15,16,19]. 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 [16,19].

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 [3]. 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 [3].

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.

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 [22]. 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 [8,22]. 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 [14,16,23–26]. 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 [25].

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 [27]. 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 [28,29] 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 [30]. 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 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) is automatically generated by the database together with several other charts. This new epidemic detection method is explained further in Box 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.

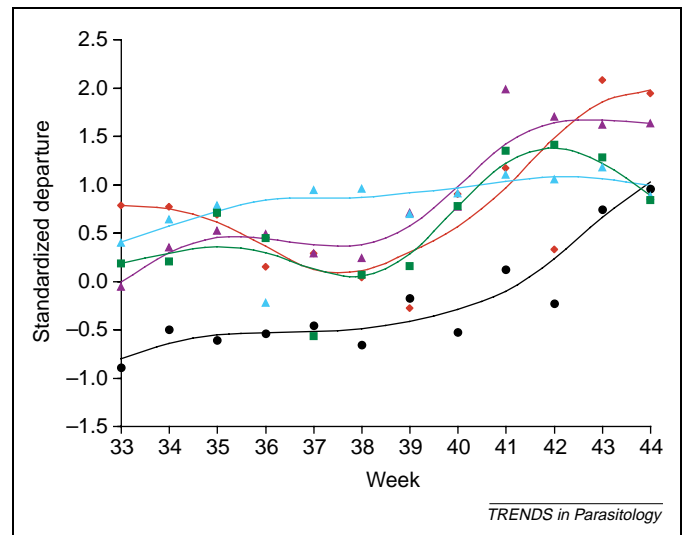


Figure 1. Standardized departure from expected number of clinical malaria outpatients during Week 33 to Week 44 of 2003, at five sentinel health centers in the Kabale District, Uganda. The weekly points indicate the actual standardized departure values for each sentinel site and the corresponding lines have been smoothed to aid 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 1 and Figure 2.) Key: black circle, Bufundi; blue triangle, Kitanga; green square, Mparo; red diamond, Buhara; purple triangle, Bukinda.

Developing epidemic early warning systems

Various attempts have been made to use climatic/environmental, RS, entomological and morbidity data for epidemic forecasting [17,26,31–35], 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.

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.

The locality-specific longitudinal data with high temporal resolutions for meteorological, entomological and

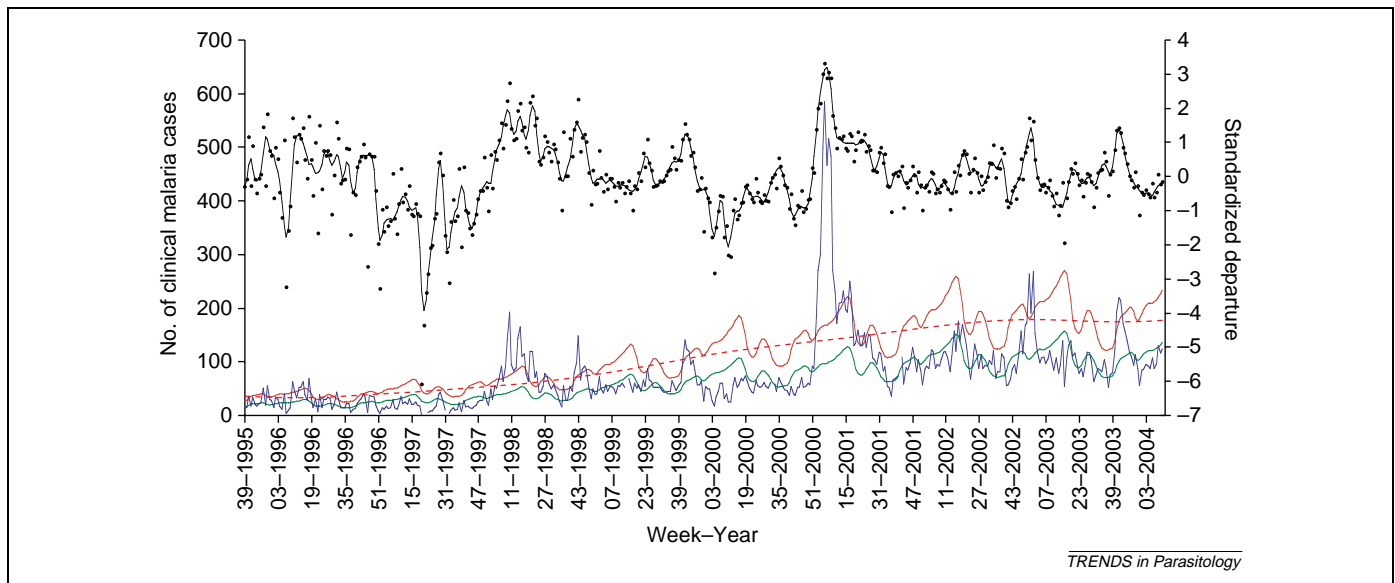


Figure 2. Historical morbidity pattern of clinical malaria between October 1995 and March 2004 at Mparo Health Centre, Kabale District, Uganda. The series shown are the observed number of cases (blue line), the expected number of cases (green line), the week-specific mean plus one standard deviation threshold (solid red line), the overall mean plus one standard deviation threshold (broken red line), and the standardized departure values (black dots with solid black 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.

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 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 [36]. 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.

Perspective

Further validation and refinement will be made to the epidemic detection techniques being implemented within

Box 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 ; $Y_t = \text{Log}_e(X_t + 1)$; \bar{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 [28,29]; and \bar{L} = overall mean of the Loess trend line values.

Then, the de-trended value corresponding to Y_t is calculated as $\hat{Y}_t = Y_t - L_t + \bar{L}$. 4253H-Twice smoothing [30] 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 ($w = 1, 2, \dots, 52$), 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 1.

Two threshold values (shown in Figure 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 , $K_t = \exp(E_{wt} + L_t - \bar{L} + S) - 1$, whereas the overall mean plus one standard deviation threshold, $\bar{K}_t = \exp(\bar{Y} + L_t - \bar{L} + S) - 1$.

Box 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.

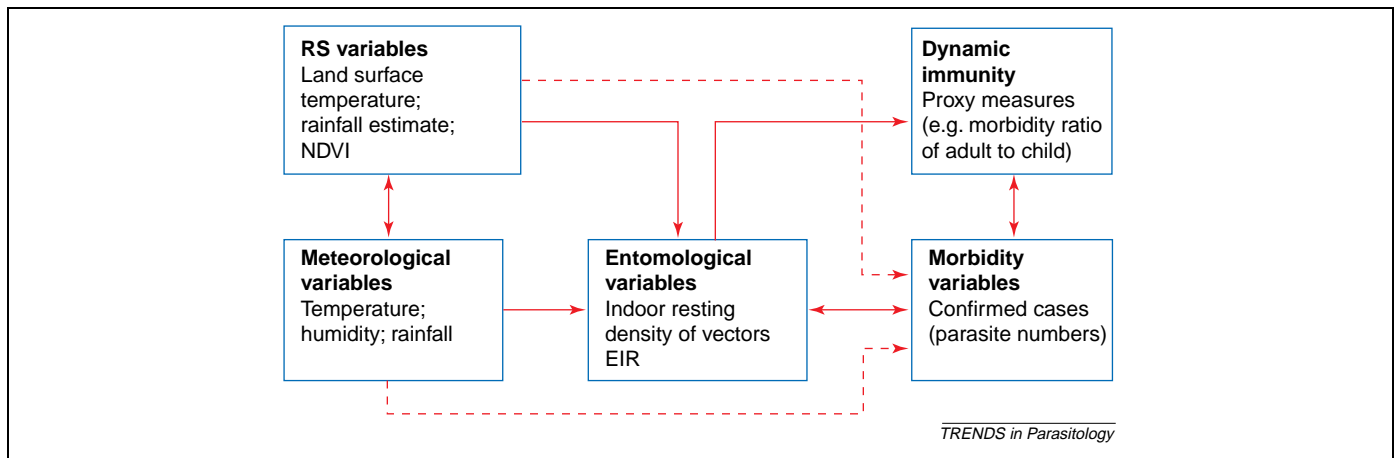


Figure 3. Epidemic-related factors and their relationships that are under investigation by the Highland Malaria Project. Prospective data are collected within the project to provide an empirical base for developing epidemic prediction models. Direct and indirect relationships between variables are represented 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.

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.

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Letters

The paradox of home management of malaria with artemisinin combinations

Derek Charlwood

Danish Bilharziasis Laboratory, Charlottenlund DK-2920, Denmark

The WHO now advocates the home management of malaria (HMM) [1]. The successful home treatment of any disease requires an educated public with access to non-counterfeit drugs from a wide variety of outlets. An educated public is particularly important when changing from one first-line drug treatment to another. The optimal scenario is that people keep complete curative courses of the drug at home in the absence of anyone being sick, therefore delays in treatment are avoided. For HMM, the most important things that people should understand are: (i) the dosage; and (ii) the need to complete treatment (it is often considered that drug resistance develops because of non-completion of treatments). Official endorsement of HMM was given initially with respect to chloroquine (CQ) but, following the almost universal development of CQ resistance (and for theoretical grounds), HMM is now being promoted for artemisinin-based combination therapy (ACT) [2]. Thus, both tactics for treatment (home versus hospital treatment) and the drug used are due for a change. ACT is faster acting, has a higher cure rate and possesses fewer side-effects than other treatments, such as CQ, but it is more expensive. Counterfeits of the cheaper antimalarial drugs already exist and they will probably be produced for ACT [3]. Unregulated outlets make it easier for counterfeit

drugs to reach an unsuspecting public, which might contribute to an increase, rather than a decrease, in mortality caused by malaria.

In urban Africa, HMM is already widely practised. ACT might be introduced to the public in these areas through television and could be sold in pharmacies. In rural areas, posters, radio programmes or plays might be used to educate the public on HMM and ACT. In addition, shops might also be used to sell ACT. Unfortunately, posters and plays have a limited value, especially when there is a change in the approach and the drug treatment used, and shops might facilitate the entry of counterfeit drugs. Hence, different approaches are needed both for education and access to ACT.

One way that this can be achieved is via 'malaria posts' where microscopic diagnosis and ACT are available. These malaria posts might also have artemisinin suppositories available (these treatments are the most likely lifesaver in the case of the high-risk groups, such as comatose children). If global funds or other outside support could establish networks of village-based simple diagnostic reference centers (such as malaria posts) that, for a limited time, diagnose malaria and can treat it with ACT for free (or at cost), then HMM will become easier to initiate. Careful education of patients should result in villagers knowing what are the correct dosages (and the consequences for themselves and their community if the treatment is or is not complied with). After a couple of

Corresponding author: Derek Charlwood (dc@bilharziasis.dk).

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