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A model structure for estimating malaria risk

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Abstract

Malaria is one of the leading causes of death in the developing world today. While prevention and treatment methods are available, their large-scale usage is a major drain on governmental budgets, and not applied whenever necessary. For this reason, understanding the endemicity of a region will allow the efficient implementation of suitable prevention methods. More importantly, the prediction of extraordinary malaria outbreaks will allow the recruitment of emergency facilities before transmission becomes widespread. In addition, climate change may influence the endemicity pattern of a region, causing malaria incidence to rise in areas in which it was non-existent or controlled. For all these purposes, a seasonal to decadal malaria forecast is needed. A novel approach has been attempted, using dynamic mathematical biological modelling. There has been initial work on the prediction of malaria epidemic based on seasonal climate forecasts, in areas of unstable transmission, which may be used to provide early warning. Here we describe a mathematical biological model of the weather-dependent parasite transmission dynamics, within-host and within-vector. The biological structure and the mathematic formulation permit computer simulation of infection patterns under various climatic and control conditions. Here we present the model structure and results at a local scale using reanalysis weather data. We then discuss the role of different aspects of the impact of unusual climatological effects and their potential implications, as well as further developments in the simulation structure and outline pathways for future progress. We also suggest further aspects of biological research, required for model improvement.
Keywords: malaria transmission; dynamic modelling; mathematical model; endemicity; Africa

Introduction

Malaria is one of the major causes of global mortality and morbidity. With an unknown number of 1 - 2.7 million patients dying annually and hundreds of millions afflicted, the need for containment and for reduction of the health burden is obvious. But due to the scarcity of resources, and the lack of a clear policy of their distribution, this control is not attained. Even though the aetiology of the disease has been known for a century (Ross 1911), the full application of this knowledge requires a practical model for a decision-making process. This model must be either robust enough to

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reflect all conditions or, preferably perhaps, flexible enough to be adaptable to local conditions. The development of such a model, and the training of the model to local conditions which can be applied to changing conditions, is a formidable task. Such a model must attempt to combine various sources of data regarding different aspects of the disease dynamics and link these aspects with external causes or covariates, which serve as driving forces or as surrogates for such forces. Due to the constant increase in empirical knowledge regarding malaria, given the international interest being drawn lately to the disease, the model should be developed in a way in which new segments of knowledge may be added into the modelling structure. Hence a modular structure is required, allowing for evaluation and updating of sub-processes, which may be defined, measured and tested in laboratory or field settings. Parameter values may thus be introduced empirically, and may be amended to reflect changes due to trends or to human intervention.

The principal malaria transmission models to date are of a few general forms. There are statistical models, which compare malaria transmission variables (such as the entomological inoculation rate, EIR) with local conditions (Killeen et al. 2000). There are rules-based models, which determine the regions in which malaria transmission is possible (Snow et al. 1998). In addition there are dynamic models relating malaria transmission to constant climate conditions (Bailey 1982). Hitherto there do not seem to have been models relating malaria transmission to changing weather, and which hence may serve for decision-making based on weather forecasts, nor in the evaluation of the impact of public-health effects on transmission dynamics in a varying climate.

The present report wishes to fill part of the niche with some of the basic groundwork towards a complete numerical model for the weather-based epidemiology of *falciparum* malaria. The report will present a simple model of malaria transmission dynamics, and then present the results of variation of model values to determine the robustness of the structure. It will then suggest various ways of evaluating the impact of intervention policies, and some simple pictures of minor climate change and potential impact on clinical incidence.

Materials and methods

The basic structure of the model and its mathematical formulation will be published elsewhere (Hoshen and Morse 2004) and will only be highlighted here. The model is based on the full dynamics of the host–vector–parasite triangle depicted graphically in Figure 1.

We must differentiate between human (hepatic and erythrocytic stages) and mosquito infection (sporogonic cycle) dynamics, while the mosquito life (gonotrophic) cycle must also be taken into consideration. The human life cycle is less important as human life expectancy is many times longer than the duration of infection. Human malaria-related mortality is rarely a significant fraction of the total population.

The parasite life cycle, with human asexual and vector sexual sections, is presented in Figure 2. Both humans and mosquitoes may be infected by parasites. The human infection is transmitted by anophelean mosquito bites and the mosquito infection transmitted by biting of humans. No direct transmission is possible between mosquitoes or between humans.

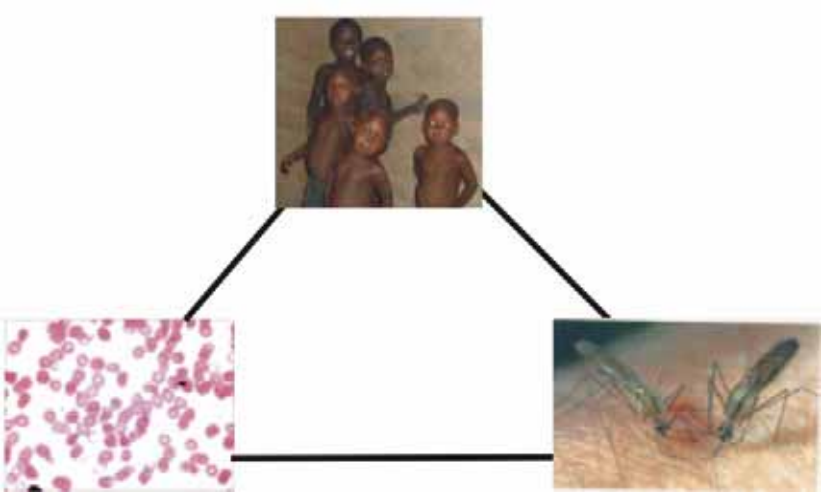

Figure 1. The disease interaction triangle: human host, *Anopheles* vector and *Plasmidum* parasite (shown in human blood sample)

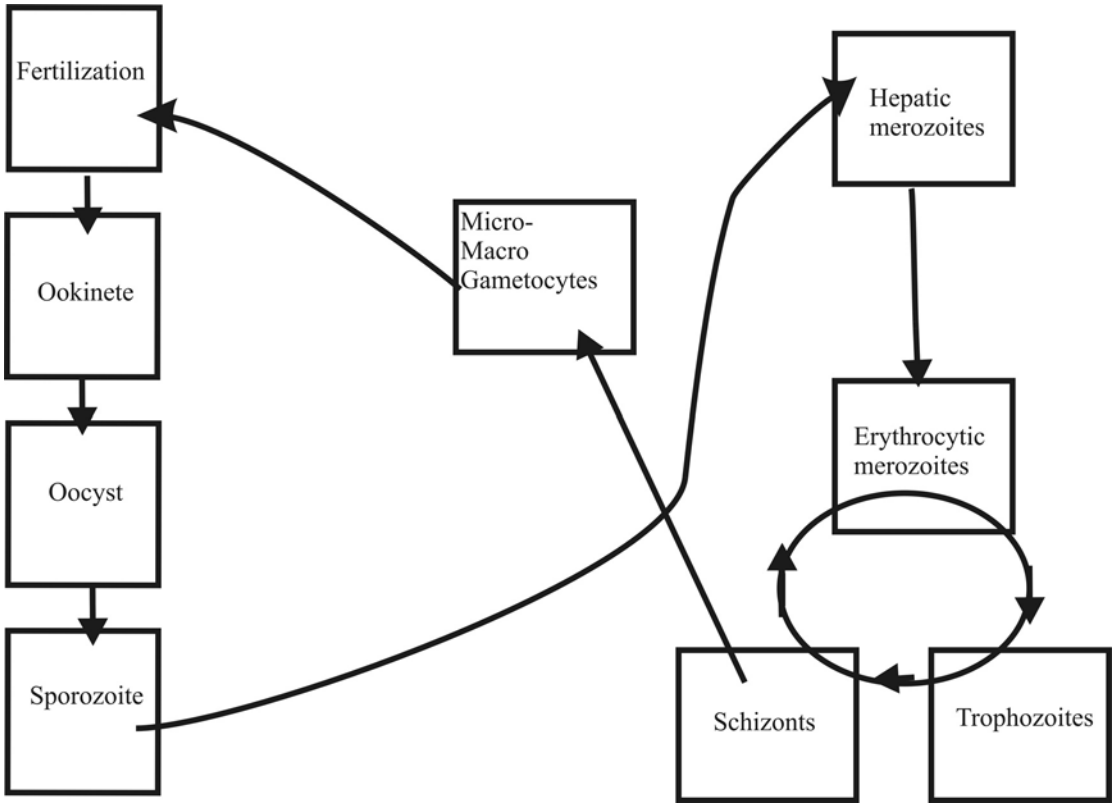

Figure 2. The parasite life cycle. The sexual (vector) stage is depicted on the left side, while the asexual (human) stage is on the right side. For intra-organism development time direction is downwards. The erythrocyte stage is cyclic multiplication

Human clearance of infection is a slow process, which may last a year. It is assumed to be a first-order process. Infectious mosquitoes never clear their infection until death. Both human and vector infections take time to develop into an infectious status. The indigenous mosquito does not seem to be harmed by the infection, but non-immune humans may die or be severely sick. The impact of immunity on severity of human infection is complex. In many cases, such as when infection is constant, the

infection is asymptomatic (thus 'healthy' individuals may be carriers), while in cases when the infection pressure is reduced, such as after a sustained low-transmission season, morbidity and mortality increase. While the within-host parasite dynamics are weather-independent, the within-vector parasite dynamics, as well as the mosquito's life cycle (Figure 3), are weather-dependent. Both the development of the parasite within the vector (sporogonic cycle) and the progress of the gonotrophic cycle (process of biting, development of eggs and oviposition) have been modelled by the usage of degree-day dynamics (Detinova 1962). Thus the length of either cycle may be expressed as $L_C=1+D_d/(T-T_c)$, where D_d is the length of the cycle in degree days, T_c the threshold for development and T the daily average temperature. D_d is 37 and 111 degree day, and T_c is 7.7 and 18^{o}C for the gonotrophic and sporogonic cycles, respectively.

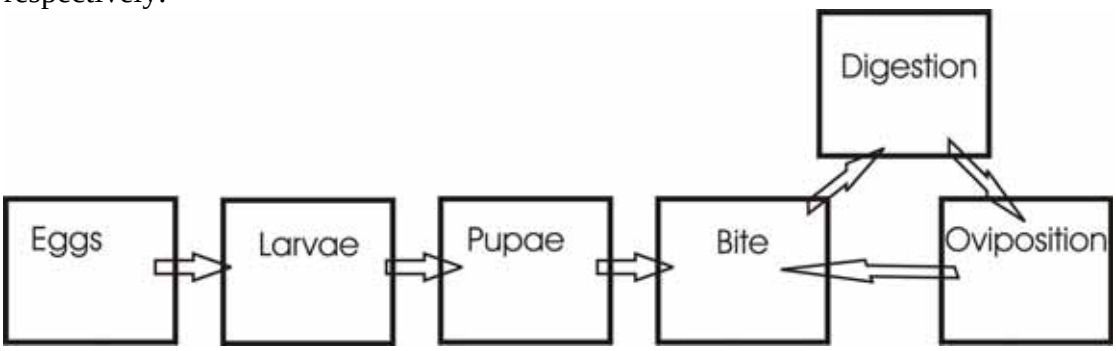

Figure 3. Schematic representation of vector development. Pre-gravid development is towards the right. Mature dynamics are cyclic

Numerous issues are still contestable in the model. Some sub-models have not been created with full empirical evidence. Some have been based on partial evidence, while in some cases we have tried to rule between two possibilities. Here we would like to investigate the sensitivity of these model processes to changes in values of parameters which seem to be crucial to the modelling of the transmission process. New field research is now underway to measure the values of these parameters in natural settings.

The daily survival of the adult *Anopheles gambiae (s.l.)* vector is temperature-dependent. It is not clear whether the survival per gonotrophic cycle is constant, save extremely high lethal temperatures, and hence the daily survival is dependent on the length of the gonotrophic cycle, with the death rate being a constant for all weather conditions (Hitherto Lindsay-Birley model, LB) (Lindsay and Birley 1996), or whether survival decreases more smoothly for higher temperatures (Martens model, MM) (Martens et al. 1995). Thus we test the output with both models, and for varying values of the LB per cycle survival α. The default value was 0.44.

For other parameters we start with values which seem to be realistic, being within empirical ranges (when determined) and producing results which are consistent with clinical reports. We then vary a single parameter at a time to establish the range that causes little change in the output. This will allow a determination of those parameters whose values have to be measured with greater accuracy.

Our model includes the following parameters (default values in brackets):

InoculationEfficiency (IE=0.9): the probability that a carrier mosquito will infect a bitten healthy human. This probability includes the probability of the inverse process. The probability of an uninfected human becoming infected is thus the number of biting infectious mosquitoes, multiplied by IE.

Host infection survival rate (0.9716). This is the daily probability that an infected human will not clear his/her infection. The default value reflects a probability of roughly 90% of an individual clearing an untreated infection within 80 days. This is consistent with reports of malariotherapy.

As oviposition is dependent on the existence of waterbodies, and *An. gambiae* usually oviposit in temporary waterbodies, such as puddles, hoofprints etc., oviposition rate is related to recent rainfall. It is, in principle, also related through evapotranspiration to temperature and humidity, and to soil type by absorption. Due to lack of data on the suitable water-balance dynamics we simplified the relation to a fixed ratio between per-mosquito per cycle oviposition to the decadal rainfall by rate constant β (1.0). This will be improved when analysis of measurements being performed now becomes available.

The Detinova model attributes different values of the gonotrophic cycle degree-day values to different humidity conditions. As we found the humidity value in our dataset was not reliable, we chose rainfall to be a surrogate for humidity. We used a single value as a threshold for transition between humid and dry conditions. In Detinova's data there are actually three different ranges of humidity, but as the intermediate and dry values are almost identical, we have elected using only two, the humid and dry conditions. The transition between them serves as a threshold (5mm).

One of the early discoveries in the modelling of malaria was the problem of the low probability of survival of mosquitoes (and hence infections) from year to year in a region of seasonal transmission. A long dry season, long hot or cold seasons can all eliminate the mosquito populations. There have been numerous discoveries which allow for the mosquito survival, either by aestivation/over-wintering in secluded hibernation locations, by delay in the maturation of eggs or mosquito long-range migration. All these processes may contribute to the re-establishment of malaria transmission. The continuation of infection dynamics in a numerical setting, when infected mosquitoes are not surviving, is enabled by the continuous influx of new infected mosquitoes, presumed waking from a period of aestivation, or new migrants. They are released into the population at a constant rate (1.00/10 days). This number is far too small to sustain malaria, except when favourable conditions for mosquito viability prevail.

Another source of reinstallation of the disease could be the arrival of new sick patients into the population (transient workers, soldiers etc.). To model this value we allow for the import of a set number (0.0) of new cases per 100 persons in the population, every 4 days.

Mosquitoes may bite both humans and cattle. This tendency is a combination of the relative abundance of cattle and the strain specific tendency. This value (0.5) is measured entomologically. As far as the model is concerned, these are wasted bites, which do not allow transmission in either direction, as cattle are not a host for *falciparum*.

As a coarse evaluation of the possible effects of climate change we varied the temperature by raising and lowering the reported temperature. We experimented with temperature changes in 1^{o}C step from -5^{o}C to $+5\ ^{o}$C from the reanalysis data. In addition we experimented with changing rainfall patterns by multiplying the rainfall values by a constant varying from 0.5 to 1.5 of the reanalysis daily rainfall.

To compare with the numerically varied weather, we have used also spatial variation, comparing with data from adjacent grid points (17.5^{o}S and 20.0^{o}S, 22.5^{o}E, 25.0^{o}E, 27.5^{o}E and 30.0^{o}E).

The purpose is to establish whether projected climate change is greater or less than spatial variation, as a determinant of malaria outbreaks.

The data is being reported graphically here. A form of numerical analysis will be developed in the future.

Results

Early 1996 and 1997 were epidemic years in the region, as a result of the heavy rains in the rain season beginning November. We would thus expect of the model prediction of high incidence. This we do indeed find in almost all runs as displayed. We would like to compare however the behaviour as determined by the various values of the parameters. To begin with, in Figure 4 we compare the Lindsay-Birley and Martens models. During rainy years the Martens-model incidence was usually proportional to the annual rainfall. In drier years, the model could not show support for incidence. The dependence on rainfall is far less clear on the various realizations of the LB model. This seems to be true for all values of the gonotrophic-cycle survival rate. In Figure 5 (see Colour pages elsewhere in this book) we compare the values given by the model using different inoculation-efficiency parameters. Perhaps not surprisingly, when the number of mosquitoes is very large (1996-9), the precise value is less important, but, when there are fewer mosquitoes (years 2000 and early 2001), transmission is highly dependent on the efficiency of the individual vector.

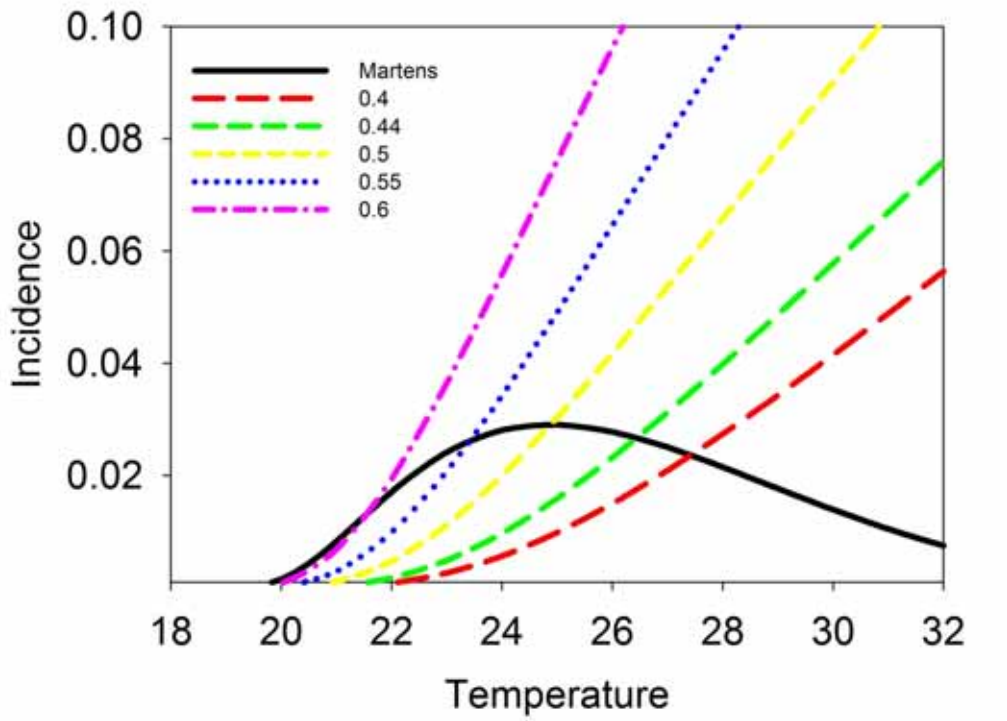

Figure 4. Comparison of Martens and Birley-Lindsay models of predicted incidence for various average temperature values. Different values of gonotrophic-cycle survival are simulated

In Figure 6 we examine the importance of the interaction between mosquito and environment. The gonotrophic-cycle length is dependent on humidity. The major importance of this parameter is in years in which the rainfall is heavy and with a double peak (1996-7 and 2000), requiring a continuation of mosquito population between rainy seasons.

In Figure 7 (see Colour pages elsewhere in this book) we compare the importance of the immune system to the dynamics of incidence. For years in which infection levels are extremely high (1999) the entire population is constantly infected, independent of the clearance rate, but in other years the clearance rate is a major determinant of the incidence rate, as the prevalence, and hence the mosquito infection rate is dependent on this parameter.

In Figure 8 we display incidence according to the model when varying the temperature by a constant shift, in this case a warming or a cooling by 1^{o}C.

In Figure 9 we present the variation of the incidence pattern for the region 17.5-20^{o}S by 22.5-30.0 ^{o}E, for gridpoints at 2.5^{o} spacing.

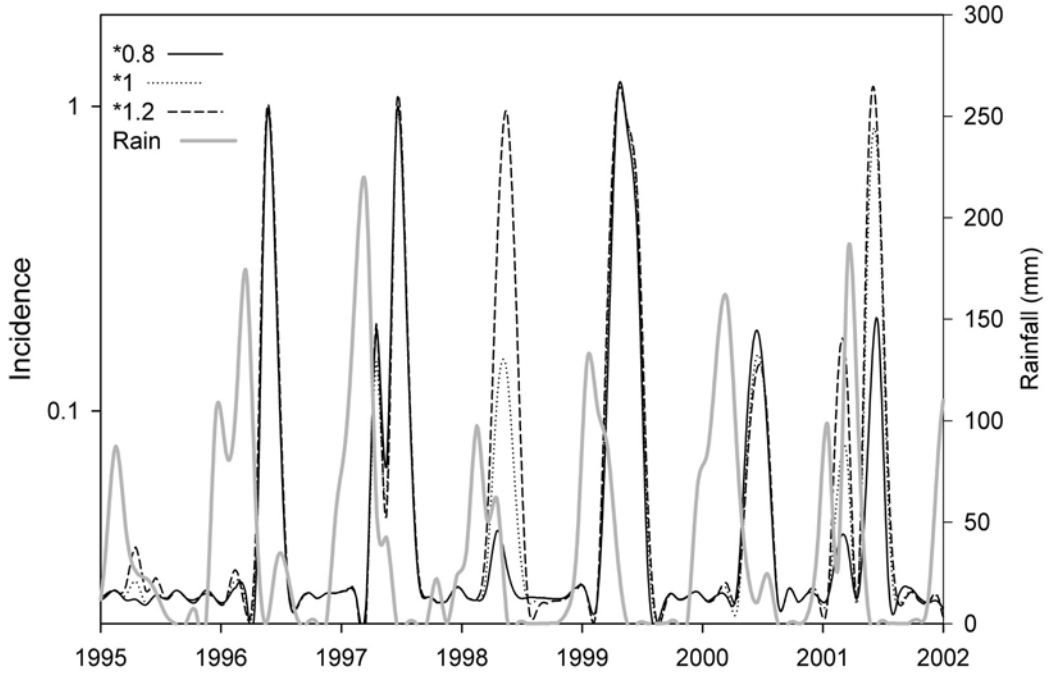

Figure 6. Sensitivity of simulated incidence to variation in rain for 17.5^{o}S 25.0^{o}E using ERA-40 weather. Calculated rainfall is multiplied by a constant (0.8, 1, 1.2) for the entire simulation

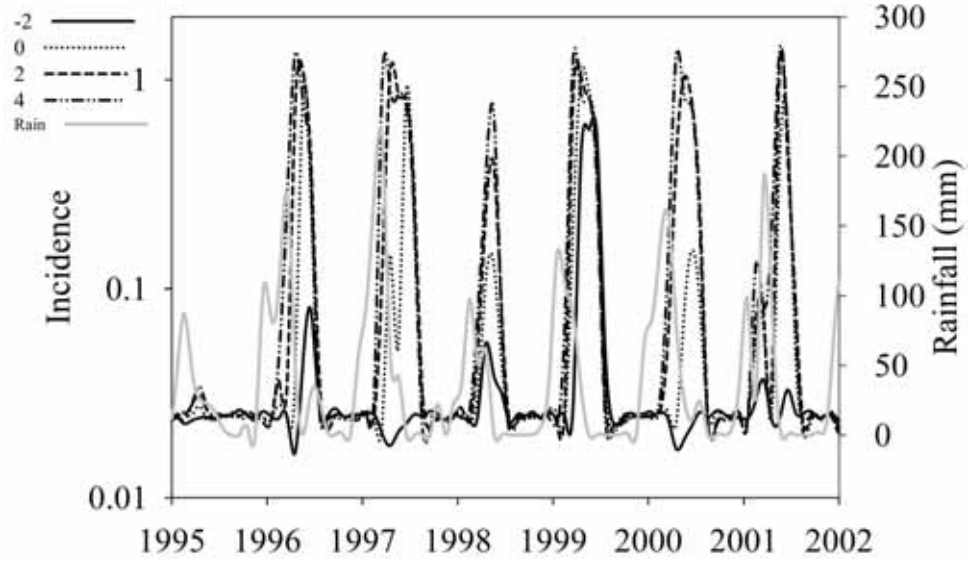

Figure 8. Sensitivity of simulated incidence to variation in temperature for 17.5^{o}S 25.0^{o}E using ERA-40 weather. Calculated temperature varied by an additive constant (-2, 0,2 ,4) for the entire simulation

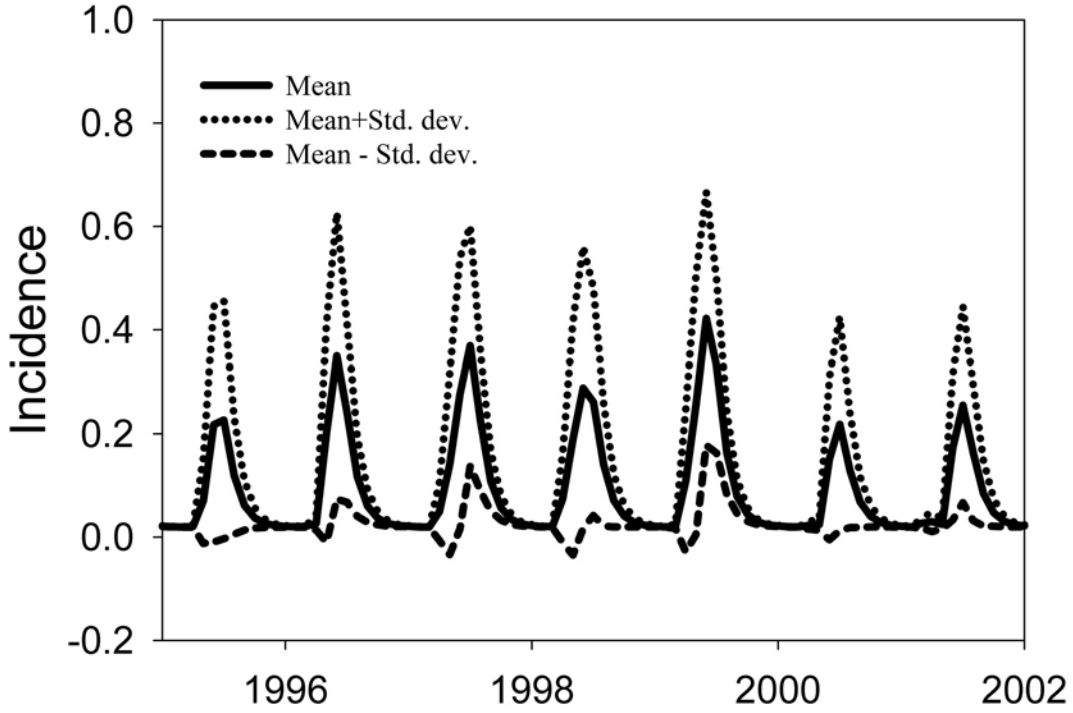

Figure 9. Variation of simulated incidence between ERA-40 grid-points. Solid line: mean of 8 grid-points. Dotted lines: mean ± standard deviation

Discussion

It seems that the complexity of the model entails the combination of many separate sub-models, each with its own parameterization. This process is obviously far from desirable, as the numerous parameters could potentially create larger variation than the weather driving force, and indeed the output of a forecast by the malaria model is dependent on the choice of model parameters. Nevertheless, if the model parameters can be optimally set, the variation is limited, and the influence of weather will be predictable. When this obstacle has been surmounted, we may utilize weather forecasts for malaria prediction.

This modelling process has a few benefits, as opposed to other methodologies, such as a scenario-based, statistical modelling method. The first is the ability to apply the method in cases substantially different from those tested. This is a special boon when attempting to establish the importance of changing climate or of the influence of extraordinary weather conditions (such as after heavy rains). Another benefit of the mathematical-biological methodology is the ability to simulate changes to entomological, parasitological or immunological aspects of the system. Thus such methods are suitable for calculating the impact of intervention policies, and thus for weighting the costs of alternative health policies, such as deciding on the cost-effectiveness of the utilization of spraying. The impact of the increased malaria prevalence in a highland area affected by global warming may be mitigated by the increased immune status. A mathematical model can readily apply such processes.

There are two possible methodologies in the usage of complex mathematical models, which are actually complimentary. One approach is to analyse the influence of a single variable (or possibly a combination) in the model output. Then we may compare the output of the entire model with clinical malaria reports. The alternative is to form a set of small experiments, each testing a single factor, in comparison with a

standard set of values. This latter was the alternative we chose. A set of experiments to establish the values of the parameters in a single setting is under way.

We find that the values of the parameters are indeed causing sizable variations in the heights and shapes of the peaks. We do find, however, that the seasonality is unchanged with variations in parameters. Weather is still the principal driver.

Weather variations can increase or reduce inter-annual variation. The fairly low temperatures at the beginning of year 2000 did not allow the development of a sizable incidence that year, independent of variations in rainfall. However, an increase of 2^{o}C is sufficient to result in an epidemic year. Variation of rainfall did not create as large variations in incidence as did temperature variation, with a clear exception in year 2001, where the first peak of the dual-peak epidemic was highly sensitive to rainfall. This leads us to understand that in this region, in which malaria is driven by the rainy season, the actual size of the epidemic is mainly determined by temperature, as the temperature is close to the development threshold.

Malaria is an environmentally driven disease and as such is highly dependent on variation in local conditions. This can be seen when we compare the conditions across Southern Africa. The inter-grid point variation in incidence is very large, as the standard variation is as large as the mean. Nevertheless, the seasonal pattern of all locations is similar. In addition, the interannual variation of the mean is similar to that of the inter-gridpoint standard deviation, reflecting the general persistence of interannual variability over the large region. Thus we find that the epidemic structure may be understood using only macro-scale information. This is quite important as climate change models work only at this scale.

We may hence conclude that the interannual variation of malaria incidence in Southern Africa is determined by both rainfall and temperature variation. The variation of temperature is of greatest importance. Thus in the case of a uniform heating of the region, we could expect the area to move from its present epidemic structure to seasonal endemicity. Unless rainfall patterns change considerably, there will be no significant change in the seasonal structure of the epidemic seasons.

Conclusion

In this short report we have presented a weather-based model of malaria transmission. We have investigated the sensitivity of the model to variations in both parameter values and weather. We have demonstrated that the interannual variation is determined by both temperature and rainfall, and that this dependence is robust to variations in parameter values. We have shown that in spite of inter-gridpoint variations, the model gives time patterns which are representative of whole regions, allowing it to serve as a basis for large-scale climate models. We have also shown that small changes in baseline temperatures will significantly increase the incidence in some otherwise non-epidemic years, an effect not found with rainfall variations.

References

Bailey, N.T.J., 1982. *The biomathematics of malaria*. Griffin, London. Biomathematics of Diseases no. 1.

Detinova, T.S., 1962. *Age-grouping methods in Diptera of medical importance: with special reference to some vectors of malaria*. World Health Organization, Geneva. World Health Organization Monograph Series no. 47.

Hoshen, M.B. and Morse, A.P., 2004. A weather-driven model of malaria transmission. *Malaria Journal*, 3 (1), 32. [http://www.malariajournal.com/content/3/1/32]

Killeen, G.F., McKenzie, F.E., Foy, B.D., et al., 2000. A simplified model for predicting malaria entomologic inoculation rates based on entomologic and parasitologic parameters relevant to control. *American Journal of Tropical Medicine and Hygiene*, 62 (5), 535-544.

Lindsay, S.W. and Birley, M.H., 1996. Climate change and malaria transmission. *Annals of Tropical Medicine and Parasitology*, 90 (6), 573-588.

Martens, W.J., Niessen, L.W., Rotmans, J., et al., 1995. Potential impact of global climate change on malaria risk. *Environmental Health Perspectives*, 103 (5), 458-464.

Ross, R., 1911. *The prevention of malaria*. John Murray, London.

Snow, R.W., Gouws, E., Omumbo, J., et al., 1998. Models to predict the intensity of *Plasmodium falciparum* transmission: applications to the burden of disease in Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 92 (6), 601-606.