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Modelling of malaria temporal variations in Iran

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Summary

OBJECTIVE To model the temporal variations in malaria episodes in a hypo-endemic area of Iran and to assess the feasibility of an epidemic early warning system.

METHODS AND MATERIALS Malaria episode data for Kahnooj District, south-east Iran, were collected from the local health system for the period 1994–2002. *Plasmodium* species-specific models were generated using Poisson regression. Starting with a simple model which included only temporal effects, we iteratively added more explanatory variables to maximize goodness of fit.

RESULTS Of 18 268 recorded malaria episodes, more than 67% were due to *P. vivax*. In addition to seasonality and secular trend, we found that incorporating a 1-month time lag between key meteorological variables and the predicted number of cases maximized goodness of fit. Maximum temperature, mean relative humidity and previous numbers of malaria cases were the most important predictors. These were included in the model with lags of no less than three dekads, i.e. three 10-day periods or effectively 1 month.

CONCLUSION Simple models based on climatic factors and information on past case numbers may be useful in improving the quality of the malaria control programme in Iran, particularly in terms of assuring accurate targeting of interventions in time and space. The models developed in this study are based on explanatory data that incorporate a lag of 1 month (i.e. data that were recorded 21–50 days previously). In practice, this translates into an operational 'window' of 1 month. Provided appropriate modes of data exchange exist between key stakeholders and appropriate systems for operational response are in place, this type of early warning information has the potential to lead to significant reductions in malaria morbidity in Iran.

keywords modelling, malaria, epidemics, prediction, early warning system, Iran

Introduction

As a result of extensive malaria control programmes over the past five decades, the burden of malaria in Iran has dropped dramatically. Malaria was endemic in most parts of Iran up to the middle of 20th century; an estimated 4–5 million people, of a population of 13 million, contracted malaria in 1924 (Manouchehri *et al.* 1992; Sadrizadeh 2001). Today, fewer than 10 000 malaria cases are detected annually. Of these, around 95% originate from south-eastern areas of the country, close to the borders of Afghanistan and Pakistan.

Even in endemic areas of Iran, malaria transmission is unstable and strongly seasonal. The majority of malaria infections occur in summer (Haghdoost 2004), with case numbers typically peaking in August and September. Winters are too cold to sustain malaria transmission, and it is usually not until April that temperature and humidity conditions become suitable for transmission. Such seasonal patterns are compounded by marked inter-annual variability in levels of transmission and disease incidence.

To date, historical temporal patterns of malaria in Iran have not been studied in detail. However, given that average climatic conditions in some malaria-endemic parts of the country are at best marginal for malaria transmission, it is highly likely that, in common with other epidemic-prone regions, inter- and intra-annual patterns of transmission are to some degree mediated by meteorological factors. In epidemic-prone areas of east Africa, for example, studies have linked inter-annual variations in malaria transmission (or the occurrence of specific epidemics) to variations in rainfall or temperature, or both (Cox *et al.* 1999; Kilian *et al.* 1999; Abeku *et al.* 2003; Teklehaimanot *et al.* 2004a), while, in west Africa, long-term changes in rainfall patterns have also been linked to apparent shifts in malaria epidemiology (Cox *et al.* 2002). While it should be recognized that climate may not always be the sole or even the most important determinant of either individual malaria epidemics or wider malaria upsurges (Hay *et al.* 2000, 2002; Cox *et al.* 2002; Checchi *et al.* 2006), an increasingly large body of evidence is emerging to suggest that climate data can, in specific epidemiological scenarios, provide important early warning information (Hay *et al.* 2003; Teklehaimanot *et al.* 2004b; Thomson *et al.* 2005; Cox & Abeku 2007). Parallel efforts are ongoing to provide public health planners with data with which relationships between disease and environment can be explored (Grover-Kopec *et al.* 2005; Hay *et al.* 2006).

Because of the high levels of temporal variability in malaria incidence experienced in Iran, the development of tools for epidemic early warning is seen as a priority by the national malaria control programme. Given the high quality of routine disease surveillance data available in Iran, it seems likely that epidemic early detection targets set by the World Health Organization (specifically the principal target that 60% of epidemics be detected within 2 weeks of onset) are achievable (Thomson *et al.* 2003, 2005; DaSilva *et al.* 2004). What is less clear is whether any added benefit (in terms of providing earlier warnings) can be achieved through modelling malaria case data in combination with climate data. Using the example of the epidemic-prone district of Kahnooj, we explore this question through the development of models of malaria incidence based on meteorological data, malaria seasonality and annual trend, and temporal autocorrelation within the surveillance dataset. The results of this exercise represent an important first step in assessing the feasibility of climate-based epidemic early warning in Iran.

Materials and methods

Study area

Kahnooj district (26.5–28.5° N, 56.9–59° E, with an area of 32 000 km^2) is situated within Kerman province in south-east Iran. It has a population of around 250 000, of which more than 70% live in rural areas. Kahnooj's climate is typically wet and cold during winter (December to April), dry and hot from May to September and warm and dry in October and November. Annually, temperatures range from highs of 45–50 °C in July to lows of 5–10 °C in January. Average annual rainfall is around 200 mm, with most rain falling in winter, followed by 7 months with almost no rain. The dominant vegetation in this area is scattered bush and scrub, with sparse tree cover. Less than 8% of the area is used for agriculture and the main crops are dates and citrus fruit.

Malaria is considered endemic in Kahnooj; 1200 and 3500 malaria cases are diagnosed each year. More than two-thirds of cases are infected with *P. vivax*. The *Anopheles* species are largely *An. culicifacies* (44%), *An. stephensi* (26%), *An. fluvuatilis* (8%), and *An. superpictus* (4%), the first two being the main malaria vectors (Haghdoost 2004). Kahnooj has a well-established malaria surveillance system. All suspected malaria cases are referred to general practitioners in the public health system by health workers and private practitioners. The national policy in Iran is that malaria should only be diagnosed using microscopy (Haghdoost *et al.* 2006a). Health workers, in both rural and urban areas, routinely take blood films from all febrile cases attending health centres. Diagnosis and treatment of malaria is free of charge in the public sector. Private practitioners do not have access to anti-malarial drugs and are required to refer all suspected cases to the public health system. An external quality control scheme is in place under the supervision of the provincial health organization (Haghdoost 2004).

Malaria data

In this study, data for all malaria cases between the 21st of March 1994 (Iranian New Year) and the end of December 2001 were collected from the district health centre. The validity of data was checked by comparing the records with the original records in rural health centres. In this dataset, the demographic information of cases, their residential address and the results of microscopic examination were recorded.

Meteorological data

The national meteorological network in Iran is linked to the World Meteorological Organisation (WMO) network and synoptic centres provide measurements for 18 meteorological variables including wet and dry bulb temperatures, humidity, rainfall, visibility and wind speed and direction. We obtained data for mean daily temperature, relative humidity and rainfall from the synoptic centre located in the centre of Kahnooj town (27.58° N, 57.42° E, elevation 470 m).

Data processing and statistical analysis

In order to link the malaria and meteorological datasets, the numbers of species-specific cases per 10-day period (dekad) and per week was computed. We chose to aggregate data by dekad, rather than by week, because much of the remotely-sensed environmental data commonly used for malaria early warning (and which may form a basis for any subsequent extrapolation of models explored in this paper) typically use this format.

Using Poisson regression models, malaria case numbers were modelled based on the explanatory variables. We found significant over-dispersion and therefore adjusted the SEs using the Huber-White ('sandwich') variance estimator. The log population was used as an offset, so the regression yields rate ratios. Seasonal and annual variations, autocorrelation between numbers of malaria cases in previous time bands, temperature, relative humidity, and annual rainfall were used as explanatory variables. Autocorrelation was included by including the number of previous cases as another explanatory variable. For this, and the climate variables, various values of the time lag were chosen, with the best-fitting one being selected. The rainfall mostly occurred during winter and there was virtually none during the transmission seasons. Therefore, we used the cumulative amount of rainfall between the previous November and two dekads ago as an explanatory variable.

Seasonality was modelled using a sinusoidal transformation of time by including both sin $(2\pi i/12)$ and cos $(2\pi i/12)$ in the regression models, where i is month number (January = 1 and so on). This corresponds to a pattern with period of 1 year, whose peak size and timing (phase) can be estimated from the regression coefficients. Annual variability was modelled based on linear and quadratic effect of year. Although there was strong co-linearity between climate variables and seasons, adding the sinusoidal transformation of time, in addition to the climate data, improved the models' goodness of fit, possibly due to the indirect impact of season on the malaria transmission, for example via life style and agriculture.

All explanatory variables were entered in the model and, using backward selection, the significant variables were kept in the final model, using a two-sided *P*-value of 0.05 as the criterion.

A model's predictive power tends to be greater on the data from which it was derived than in new data. To allow this, monthly and dekadal malaria data were allocated to two separate datasets. The first or 'modelling' dataset was taken up to and including 31 December 1999 and used for parameter estimation.

The second or 'checking' dataset was from 2000 and 2001 and used to evaluate model goodness of fit. Within this period, the predicted number of cases for each dekad was based on (a) the parameters estimated from the 'modelling' dataset and (b) the relevant data variables, which were lagged by a minimum of 3 dekads. Hence, over this period, the predicted number of cases for a given dekad is based purely on data which were available at that time. This is, therefore, a more realistic test of the accuracy of prediction. Models were generated using Stata version 8 (Stata Corporation, College Station, TX).

Results

From March 1994 to the end of 2001, 18 268 malaria episodes were recorded in Kahnooj district, of which 12 337 (67.5%) were due to *P. vivax*, 5858 (32.1%) to *P. falciparum*, and 73 (0.4%) to mixed infections.

Incorporating a three- to four-dekad lag maximized the Pearson correlation coefficient between the number of cases and meteorological variables. These associations were assessed based on the number of cases in each dekad and mean temperature and relative humidity in the preceding 1–6 dekads. Maximum associations between *P. falciparum* and meteorological variables were achieved using a four-dekad lag (temperature: $r = 0.12$, $P = 0.048$; relative humidity $r = -0.07$, $P = 0.21$), while for *P. vivax* lags of three and four dekads were optimal (temperature: $r = 0.48$, $P < 0.0001$; relative humidity $r = -0.08$, $P = 0.19$). Therefore, we modelled the number of cases based on meteorological data with a three-dekad (i.e. 1 month) gap.

A sinusoidal transformation of time, to represent seasonality, provided a more accurate description of temporal variation in case numbers for *P. vivax* than *P. falciparum* (Figures 1 and 2). The phases of these models estimated the peak of *P. vivax* case numbers around 1 month after that of *P. falciparum* (12th of July and 16th of August, respectively). Adding the linear effect of year improved model accuracies considerably, particularly for *P. falciparum* (Figures 1 and 2). In addition to the effects of seasonality and time trend, meteorological factors explained a significant amount of malaria variation (Wald test: $P < 0.001$).

Including information on the recent levels of malaria incidence (represented by the monthly number of malaria cases, recorded 2 months prior) further improved model accuracy (Wald test: $P < 0.01$, Figures 1 and 2). Nevertheless, after dropping variables by backward selection, the only remaining significant variables were sinusoidal seasonal effect, linear effect of year, lagged maximum temperature and humidity and the lagged number of malaria cases (Table 1).

Based on the results of these models, each species had a decreasing secular trend, this being more prominent for *P. falciparum* (the risk ratios were 0.94 and 0.67 per year, for *P. vivax* and *P. falciparum*, respectively). Temperature was positively associated with the risk of disease in both species. This is likely to reflect inactivity of adult mosquitoes at lower temperatures. However, the negative association between risk and humidity is less intuitive (we return to this in the discussion). Finally, the number of cases in previous weeks was associated with current risk. This is likely to be just a reflection of autocorrelation in

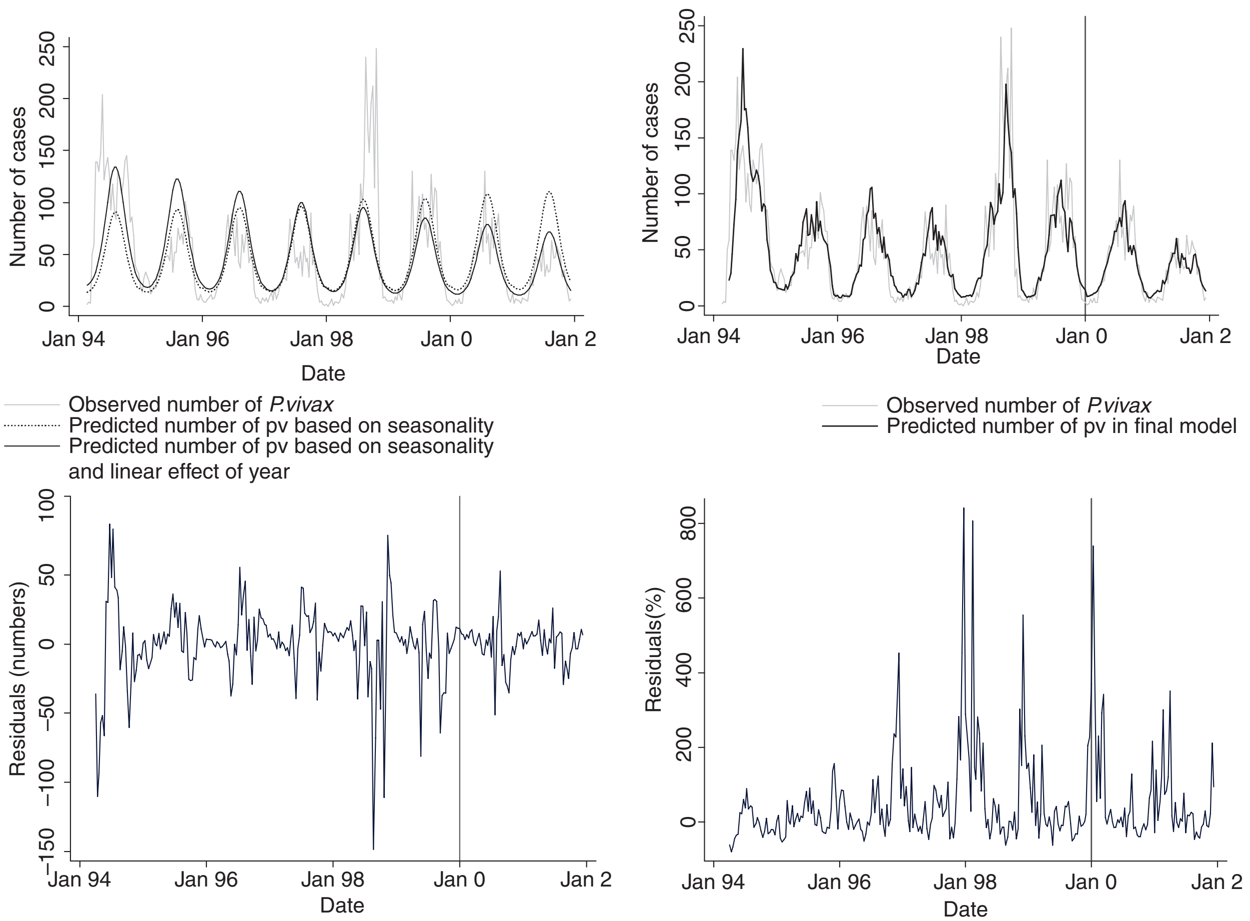

Figure 1 The observed and the predicted numbers of *P. vivax* cases from two different models (top graphs). The top left graph shows a model based on sine transformation of time and linear effect of year. For the top right graph maximum temperature and humidity lagged by 3 dekads and the total number of cases occurring in dekads at lags 3, 4 and 5 were added to the model. The bottom graphs show the discrepancy between observed and predicted values ('residuals') for the model shown in the top right graph. The bottom left graph shows the residual in terms of absolute number of cases (predicted minus observed, so that negative values reflect under-prediction), and the bottom right graph in terms of percent. Each model was created by fitting to the data up to 31 December 1999 (vertical line), then applied to the data of 2000 and 2001.

Table 1 Final models for incidence of number of *P. vivax* and *P. falciparum* cases, based on the 'modelling' dataset (21 March 1994 to 31 December 1999)

	P. vivax		*P. falciparum*	
Explanatory variables	Risk ratio	*P*-value	Risk ratio	*P*-value
Sine transform of time	0.69	<0.0001	0.57	<0.0001
Linear effect of year	0.94	<0.0001	0.67	<0.0001
Mean daily maximum temperature, lagged by 3 dekads (per tenth of a degree Celsius)	1.34	<0.0001	1.16	0.03
Mean daily humidity, lagged by 3 dekads (per percentage point)	0.9	0.002	0.87	0.001
Total of cases occurring in dekads at lags 3, 4 and 5	1.003	<0.0001	1.002	<0.0001

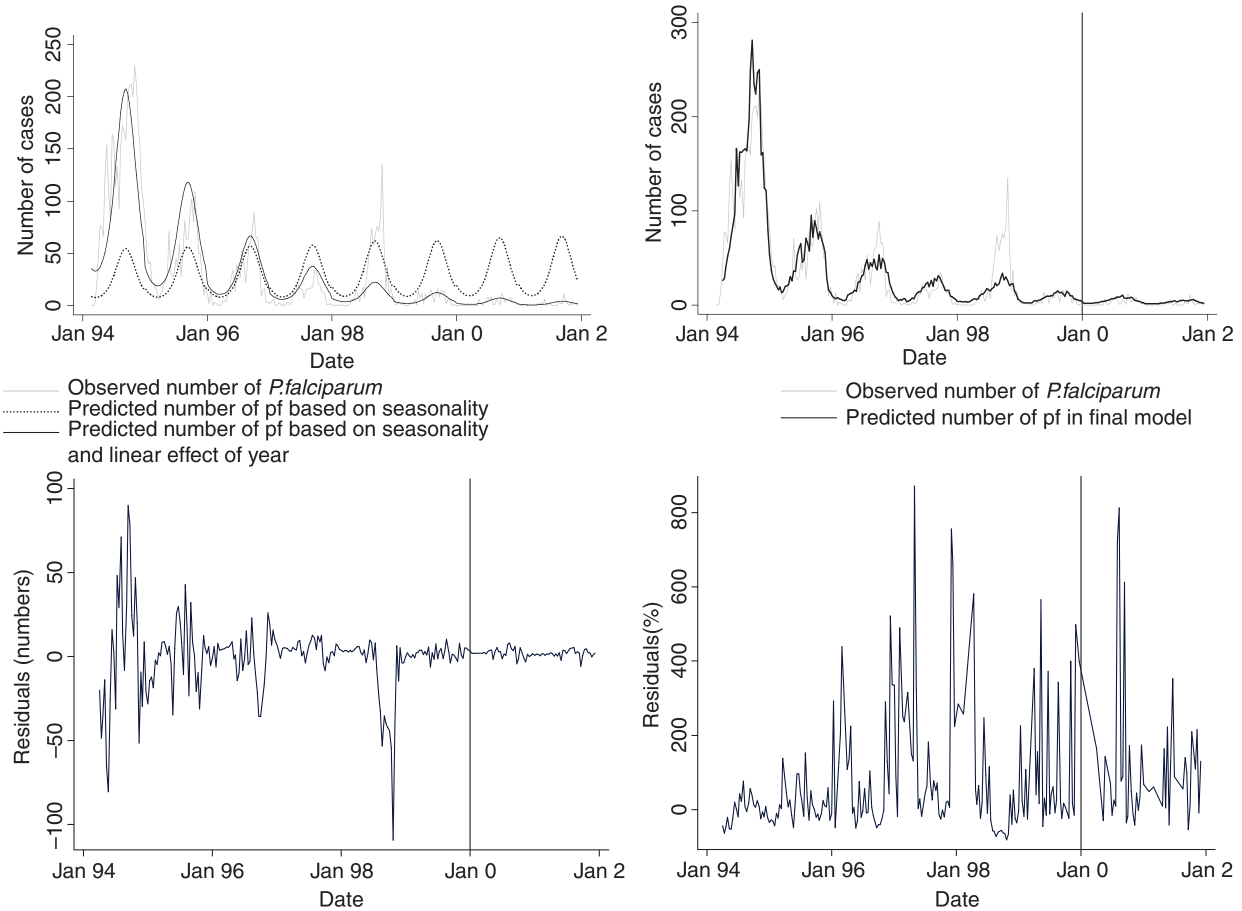

Figure 2 The observed and the predicted numbers of *P. falciparum* cases from two different models (top graphs). The top left graph shows a model based on sine transformation of time and linear effect of year. For the top right graph maximum temperature and humidity lagged by 3 dekads and the total number of cases occurring in dekads at lags 3, 4 and 5 were added to the model. The bottom graphs show the discrepancy between observed and predicted values ('residuals') for the model shown in the top right graph. The bottom left graph shows the residual in terms of absolute number of cases (predicted minus observed, so that negative values reflect under-prediction), and the bottom right graph in terms of percent. Each model was created by fitting to the data up to 31 December 1999 (vertical line), then applied to the data of 2000 and 2001.

incidence, i.e. the presence of peaks or troughs of several weeks' duration, beyond those expected from the average several variation.

The magnitude of discrepancy between observed and predicted values from this model is shown in Figure 2. Treating positive and negative errors equally, the mean percent errors were 50.3 and 68.5 for *P. vivax* and *P. falciparum*, respectively, for the period 1994 to 2000, using the model which was fitted to those same data. When the model was extrapolated to the period 2001–2002, the average percent errors were 68.3 and 89.7 for *P. vivax* and *P. falciparum*, respectively. Figures 1 and 2 do not show obvious systematic changes over time, except for one period of poor performance for each species. For both species, this occurs in 1998. We return to this period in the discussion. The model for *P. falciparum* gave over-estimations more commonly than underestimations (69% of dekads over-estimated compared with 31% underestimated), while these proportions were more equal for *P. vivax* (58%:42%).

Discussion

Our analysis indicated that, on its own, seasonality explained a considerable part of the temporal variation in malaria incidence, particularly for *P. vivax*. Adding the effects of linear time trend improved the goodness of fit of models for both species, but more so for *P. falciparum*. Incorporating climate data further improved model accuracies. Autocorrelation between the numbers of cases in consecutive dekads also proved to be important. None of the variables by itself generated a valid model. However, the combination of variables generated more or less accurate ones. Therefore, we recommend using all easily available explanatory variables to improve the goodness of fit of models. In addition, we found fairly different models for *P. vivax* and *P. falciparum*. Hence, we recommend using species-specific predictive models.

The positive association between the risk of malaria and temperature (Table 1) was unsurprising. However, the negative association with humidity is less intuitive. One explanation could be that mosquitoes find domestic environments relatively favourable when humidity reduces. Exploration of this would require more detailed work on mosquito behaviour in the area. It could also prove useful to measure climatic variables at a finer scale than that of district, possibly via remote sensing (see below).

We applied the parameters estimated from the first 5 years' data to those of the last 2 years, to check how well they could predict the number of malaria cases. The findings showed that the underestimations of models were more or less acceptable, although the over-estimation in the *P. falciparum* model was nearly high; implied that such a model is sensitive but not specific.

As the discrimination between new *P. vivax* infection and relapse is nearly impossible in the field, we modelled numbers of all cases. The relapse rate of *P. vivax* was considerable in Kahnooj (Haghdoost *et al.* 2006b), therefore, some part of the residuals in the *P. vivax* models might be partly due to such a limitation. Nevertheless, the goodness of fit of our *P. vivax* models suggests that they could contribute to an early warning system in the field.

Our final models predict case numbers on the basis of environmental conditions and case numbers recorded 1 month earlier, which in effect provides a maximum operational early warning of 1 month. Although it is likely that additional accuracy could be obtained by incorporating environmental and case data from the month immediately preceding each prediction (1–30 days earlier) (Abeku *et al.* 2004a), it is doubtful whether such data could be practically and routinely incorporated in an operational early warning system, or that the resultant lead times would be sufficiently long to allow the implementation of effective response measures.

From a practical standpoint, an early warning lead time of 1 month (using data from 21 to 50 days earlier) is probably sufficient for the planning and implementation of specific measures such as mass drug administration or mass fever treatment (Abeku 2007). However, unless the warning signals that are produced from an epidemic early warning system are clearly linked to specific operational responses, there is a high risk that early warnings will have a negligible impact on the course of individual outbreaks (Cox *et al.* 2007). It is also essential that malaria control decisions that result from early warning systems take into account the inherent uncertainty associated with predicting malaria transmission. For example, while it might not necessarily be appropriate to directly implement specific interventions on the basis of outputs from the type of model explored here, appropriate forms of response may include: (i) ensuring that diagnostic services and surveillance activities are fully operational in epidemic-prone areas, and that local and national stocks of anti-malarial drugs are sufficient; (ii) doing rapid field assessments to confirm the scale and geographical extent of the outbreaks (s); and (iii) sensitizing communities in high-risk areas.

Although our models predicted the temporal variations precisely in most years, they did not predict a major outbreak in 1998. Although we could not find any prognosis of that outbreak in our explanatory variables, local expert opinion has linked the outbreak to political instability in Afghanistan, which led to marked increases in the number of illegal immigrants entering Iran in 1997 and 1998 (Haghdoost 2004). From a programmatic perspective, it is therefore important that comprehensive assessments of epidemic risk incorporate not only information on climate and preceding case numbers, but also a more general assessment of population vulnerability using indicators that are locally appropriate (WHO/RBM 2001).

Although the results of the current modelling exercise are encouraging, a number of scientific and practical issues need to be considered before any uptake of these tools can be considered. First, it should be recognized that the models presented here incorporate high-quality meteorological data from a synoptic station located in the study area. In an operational setting, it is doubtful whether such locally-representative meteorological data would be available for all epidemic-prone localities. In addition, although data availability does not appear to be an issue in Iran, in many countries, the sharing of meteorological data across government sectors is a slow and difficult process. In these situations, it is unlikely that data required as input to early warning models would be obtainable in a sufficiently timely or routine manner to be used for 'real-time' modelling. Moreover, although the use of single station data in geographically-specific models is relatively straightforward, the process of interpolating data between these points requires the use of sophisticated algorithms. In addition, where stations are sparsely distributed, the validity of interpolated estimates may be questionable. For these reasons, proxy meteorological and vegetation indicators derived from satellite remote sensing data may, in many cases, represent a relatively cost-effective, reliable and reproducible way to generate the necessary model inputs for early warning (Hay & Lennon 1999). Future research should more fully explore these alternative datasets.

From the perspective of implementation, the extent to which early warning models of this type should replace, or, alternatively, be used in parallel with ongoing routine epidemic monitoring activities also requires consideration. The current epidemic monitoring system in Iran was established using graphs displaying the mean incidence of malaria over the previous 5 years compiled from malaria surveillance data. This system is very simple and is straightforward to apply – but at the same time has limitations and clearly cannot easily incorporate environmental early warning information. In other epidemic-prone areas, operational research has addressed the feasibility of computer-based surveillance operations, where responsibilities for data collation, analysis and interpretation can be devolved to district-level teams (Abeku *et al.* 2004b). If Iran is to move towards more comprehensive systems for epidemic early warning, detection and response, it is likely that similar systems will need to be considered.

Our models are based on a lag of 1 month, which corresponds to a lead time long enough to permit planning by health services. If linked with efficient information exchange and coordinated responses, an early warning system derived from these findings could lead to significant reductions in malaria morbidity in Iran.

Conclusion

We suggest using such species-specific models with a range of predictors — including climatic variables — which are easily available in the field for the prediction of malaria. Our findings show the utility of such models and suggest their development for early warning systems in Iran and possibly other Middle East countries with comparable epidemiological patterns.

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