

Mapping and predicting malaria transmission in the People's Republic of China, using integrated biology-driven and statistical models

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Abstract. The purpose of this study was to deepen our understanding of *Plasmodium vivax* malaria transmission patterns in the People's Republic of China (P.R. China). An integrated modeling approach was employed, combining biological and statistical models. A Delphi approach was used to determine environmental factors that govern malaria transmission. Key factors identified (i.e. temperature, rainfall and relative humidity) were utilized for subsequent mapping and modeling purposes. Yearly growing degree days, annual rainfall and effective yearly relative humidity were extracted from a 15-year time series (1981-1995) of daily environmental data readily available for 676 locations in P.R. China. A suite of eight multinomial regression models, ranging from the null model to a fully saturated one were constructed. Two different information criteria were used for model ranking, namely the corrected Akaike's information criterion and the Bayesian information criterion. Mapping was based on model output data, facilitated by using ArcGIS software. Temperature was found to be the most important environmental factor, followed by rainfall and relative humidity in the Delphi evaluation. However, relative humidity was found to be more important than rainfall and temperature in the ranking list according to the three single environmental factor regression models. We conclude that the distribution of the mosquito vector is mainly related to relative humidity, which thus determines the extent of malaria transmission. However, in regions with relative humidity >60%, temperature is the major driver of malaria transmission intensity. By integrating biology-driven models with statistical regression models, reliable risk maps indicating the distribution of transmission and the intensity can be produced. In a next step, we propose to integrate social and health systems factors into our modeling approach, which should provide a platform for rigorous surveillance and monitoring progress towards *P. vivax* malaria elimination in P.R. China.

Keywords: *Plasmodium vivax*, malaria transmission, environmental factor, biology-driven model, statistical model, People's Republic of China

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Introduction

From a global public health point of view, malaria is the most important vector-borne disease (WHO, 2009). Malaria is caused by the protozoan *Plasmodium* spp., and the disease has been a human

scourge since ancient times, mainly in tropical and subtropical regions of the Americas, Asia and Africa (Gratz, 1999; Carter and Mendis, 2002). The annual incidence of clinical malaria episodes due to *Plasmodium falciparum* is 300-660 millions (Snow et al., 2005), whereas 130-435 million episodes of clinical *P. vivax* malaria occur annually (Hay et al., 2004). Malaria still kills approximately 1 million individuals each year, the majority of whom are children below the age of 5 years in sub-Saharan Africa (Hay et al., 2004; Lopez et al., 2006; Brooker et al., 2008). At present, over 80% of all malaria-related deaths and global burden due to malaria are concentrated in sub-Saharan Africa (Hay et al., 2000, 2004; Lopez et al., 2006; WHO, 2009).

Malaria spans a multitude of climatic zones in the east of Asia, from the frigid temperate to the torrid. The endemic regions in the People's Republic of China (P.R. China), which covers approximately 5,200 km from east to west and 5,500 km from north to south, are mainly located south of 45° N latitude (Zhou, 1991). References to periodic fevers that are characteristic for malaria can be found in the Chinese medical literature as far back as 2,700 BC (Cox, 2002). In ancient times, the provinces of Yunnan, Guangxi and Fujian were named the "miasma region" due to the many malaria cases that occurred there. After 1949, owing to the launch of a national malaria control programme and other contextual determinants, the endemic situation of malaria improved considerably, particularly with regard to *P. falciparum* infection (Ho, 1965). *P. vivax*, on the other hand, proved more difficult to control owing to the liver-stages, hypnozoites resulting in relapses years after infections occurred (Wang et al., 2005). Indeed, two large-scale outbreaks of *P. vivax* malaria occurred in the early 1960s and 1970s with an estimated number of 10 million and 21 million cases, respectively, with corresponding prevalence figures around 1.5% and 3% (Tang et al., 1991). Subsequently, control efforts were enhanced, and the number of malaria cases decreased markedly between 1970 and 1990. On

average, the annual reduction rate was 23%, to reach a low of 117,000 cases in 1990 (Tang et al., 1991). However, the challenge persisted and the problem of *P. vivax* malaria started to re-emerge, explained by increased population movement, development and spread of drug resistance, shortage of funds or respective allocations leading to weakened professional malaria teams, and general neglect of *P. vivax* (Baird, 2007). In addition, climate changes led to higher transmission capacity of *Anopheles*. In the 1990s, new transmission foci appeared in P.R. China and more intense transmission became obvious by 1994 (Tang et al., 1991; Zhou, 1991; Liu et al., 1995).

Geographical information systems (GIS) and remote sensing from earth-observing satellites have facilitated epidemiological research pertaining to vector-borne, parasitic diseases and led to improved aptitudes for spatially-explicit risk profiling and early warning systems (Hay et al., 2000; Bergquist, 2001; Raso et al., 2009; Yang et al., 2010). In turn, these advances have contributed to a growing trend of modeling as a valid approach to predict future disease transmission. The models can be divided into two categories, namely (i) deterministic models, and (ii) mathematical and statistical models (Malone, 2005; Peterson, 2006; Wu and Wu, 2006; Ouyang et al., 2009; Yang et al., 2010). The former, usually called biology-driven models, rely on biological data and meteorological variables collected by ground-based or satellite-derived observations. These models are based on the study of how important biological indicators are influenced by climatic factors such as temperature and rainfall, among others. Typical examples are the minimum and maximum thermal thresholds for the survival of infectious agents developing in a vector or an intermediate host (Malone, 2005; Peterson, 2006). The mathematical statistical approach, on the other hand, requires the development of a new, weather-dependent mathematical dynamic model, which takes into account known risk factors quantitatively (Yang et al., 2005, 2008; Galardo et al.,

2009). The various statistical models rely on various mathematical approaches to quantitatively investigate the linkage between risk factors and disease prevalence or incidence. A multitude of such models have been developed, for example logistic multi-factor regression or Bayesian spatial models. Both biology-driven and mathematical models have been employed for the identification of major determinants of disease transmission and for the prediction of future transmission trends (Hales et al., 2002; Yang et al., 2005, 2010; Riedel et al., 2010).

In recent years, biology-driven and statistical models have been developed to improve our understanding of a likely impact of climate change on malaria transmission. For example, Craig et al. (1999) developed a fuzzy-logic, climate-based distribution model and the authors suggested that such a model can be used to study the impact of climate change on malaria transmission. Combined with population, morbidity and mortality data, this approach can be utilised to estimate the burden of disease and aid the strategy of malaria control. Using a regression approach, Hay et al. (2002) analysed the potential effects of climate change on highland malaria, while Rogers and Randolph (2000) used a statistical model to predict the global impact of climate change on malaria distribution.

Thus far, only a few attempts have been made to integrate the two modeling approaches to forecast malaria transmission in a future warmer world. To deepen our understanding of transmission patterns and risk for *P. vivax* malaria epidemics in P.R. China, we employed an integrated modeling approach. Hence, we combined biology-driven and statistical models by using information-theoretical methods (Burnham and Anderson, 2004; McCarthy, 2007) along with GIS techniques. Our specific objectives were to (i) identify key environmental risk factors that govern malaria transmission; (ii) predict the transmission intensity and potential risk areas of *P. vivax* malaria in P.R. China; (iii) pinpoint the high-transmission regions;

and (iv) contribute to a practical guide for malaria control in the field.

Material and methods

Digital map

The Digital Map Database of P.R. China (DMDC), readily available at a scale of 1:1,000,000 (National Bureau of Surveying & Mapping, P.R. China), was used as background for the disease mapping.

Environmental data

Daily environmental data, specifically average temperature, rainfall and relative humidity (RH), were obtained from 676 locations that are displayed on Figure 1. The environmental data covered a 15-year time series from 1981 to 1995, and were provided by the Chinese Meteorological Administration (<http://www.cma.gov.cn>). The long-term, averaged annual, environmental data were determined as detailed below.

Temperature. Any organism (e.g. insect, parasitic protozoan or helminth), relying on a successful passage through different developmental stages (life forms) requires a certain amount of thermal energy to develop from one stage to another in its life cycle. This amount of heat can be expressed in units termed “growing degree days” (GDD). The yearly GDD (YGDD) thus represents the accumulated, thermal energy in a specific location and when the YGDD value, divided by the GDD (required for completing one life cycle of a particular organism), exceeds 1, it follows that the respective location is suitable for the organism in question. According to this logic, the YGDD for each *P. vivax* location can be calculated by equation (1):

$$YGDD = \frac{\sum_{y=1}^{15} \sum_{d=1}^{365} (T_{daily} - 14.9)}{15} \quad (1)$$

where T_{daily} signifies the daily mean temperature. The value 14.9 in equation (1) indicates the lowest

temperature required for the development by *P. vivax* in the *Anopheles* mosquito vector. Values of the term “ $(T_{daily} - 14.9) < 0$ ” should be treated as 0.

Rainfall. The yearly rainfall was calculated according to equation (2):

$$Rainfall_{year} = \frac{\sum_{\tau} \sum_{\tau}^{15} Rain_{daily}}{15} \quad (2)$$

Relative humidity (RH). According to historical records, the vector of *P. vivax* primarily occurs in regions where RH exceeds 60%. Therefore, the effective yearly RH (YRH) was calculated according to equation (3):

$$YRH = \frac{\sum_{\tau} \sum_{\tau}^{15} (RH_{daily} - 60)}{15} \quad (3)$$

where RH_{daily} signifies the daily RH. Values of the term “ $(RH_{daily} - 60) < 0$ ” were treated as 0.

Malaria-endemic data

The map of malaria distribution published in 1995 (Liu et al., 1995) reflects the long-term malaria

transmission status. The 676 locations on the map were classified into four strata, namely (i) non-endemic; (ii) sporadic-endemic; (iii) meso-endemic; and (iv) hypo-endemic (Fig. 1).

Weighting environmental factors using a Delphi approach

This evaluation was done to determine the initial selection of environmental factors based on four sequential steps (Fig. 2). First, we designed and pre-tested a questionnaire. Second, we selected key informants (i.e. knowledgeable staff from malaria control stations) and invited them to fill-in our questionnaire. Third, the filled-in questionnaires were collected by our research team. Fourth, the questionnaire results were double-entered, cross-checked and then analyzed for parameters ranking and weighting.

Data obtained through the questionnaire survey were key ecological and environmental features in connection with *P. vivax* transmission, including parameters such as temperature, rainfall, RH, wind velocity inclusive of general topography and ecology such as elevation, soil type, vegetation and presence of water bodies. Overall, 39 questionnaires

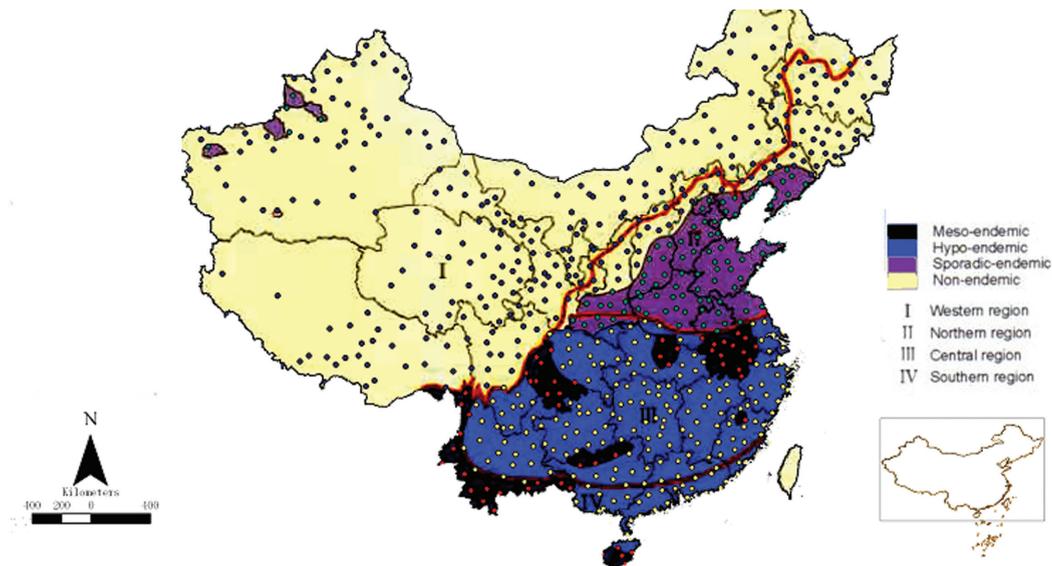


Fig. 1. The malaria endemic situation in P.R. China in 1995 and the 676 observing stations located in four different strata of endemicity areas of malaria.

were distributed, 23 of which were returned in the first round. Despite this relatively low compliance rate (59%), bias is likely to be minimal, as those key informants who returned the questionnaires showed a wide geographical distribution, representing 16 institutions from 13 provinces. Of the study participants, two-thirds were senior specialists with experience of this type of data collection.

Based on the results of the first round evaluation and analysis, a second round Delphi evaluation was carried out, adhering to the same process. The weights of the main environmental factors governing malaria transmission were calculated for each round. The same 23 participants in the study who had responded in the first round were re-contacted and all of them completed and returned our questionnaire. Thus, the study was based on information from 23 key informants from a large variety of geographical areas.

Disease mapping according to a biology-driven model

The mapping of environmental risk factors for *P. vivax* malaria was done using version 9.1 of the ArcGIS software (ESRI; Redlands, CA, USA). Ordinary kriging, using geostatistical analysis, was

applied to generate a smoothed surface map of the YGDD, rainfall and YRH. The surface maps depicting YGDD, rainfall and YRH were re-classified into 10 classes.

The malaria prediction map was overlaid by the three classified environmental factors according to the contribution of each factor derived from the Delphi evaluation.

Model comparison based on statistical analysis

The multinomial, logistic regression model was chosen since the parameters involved are polytomous, i.e. non-, sporadic-, meso- and hypo-endemic. Based on the results of the Delphi evaluation, only three environmental factors were used in the model; those that were most frequently stated by the experts. A suite of eight models ranging from null model to a fully saturated one were constructed as follows:

$$Multi(p[], N) = \beta_0 + \beta^* E + \varepsilon_t, \tag{4}$$

$$\varepsilon_t \sim Normal(0, \sigma^2)$$

where $p[]$ signifies the probability of each type of endemic situation to exist, N denotes the total number of observing stations,

$$\beta = \begin{pmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_n \end{pmatrix},$$

E is the vector of environmental factors ($E1, E2, E3$) and ε_t represents unexplained residual error.

All models were fitted using maximum-likelihood estimation and analyses were done using the R Package, version 2.4.0 (R Development Core Team, 2004). Model comparisons were based on multi-model inference (MMI) using two different methods. First, Akaike's information criterion (AIC), corrected for small sample sizes (AICc) as an estimate of Kullback-Leibler (K-L) information loss (Akaike, 1973; Burnham and Anderson, 2002); and second

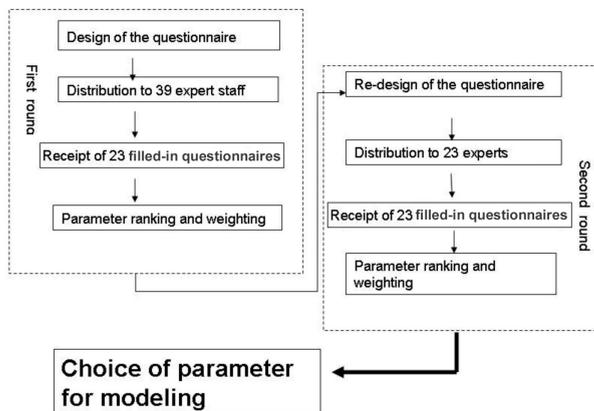


Fig. 2. Flow chart depicting the 2-step Delphi evaluation process employed in the current study.

the dimension-consistent Bayesian information criteria (BIC) as an estimate of the Bayesian odds ratio (Link and Barker, 2006). For AICc and BIC, we calculated the difference between the model's criterion and the top-ranked model (Δ_i) and the relative model weight (w_i) (Link and Barker, 2006). Thus, the strength of evidence ($wAICc$, $wBIC$) for any particular model varies from 0 (no support) to 1 (complete support) relative to the entire model set. The percentage of explained deviance was calculated by contrasting with the null model.

Results

Environmental factor weights by Delphi evaluation

In-depth analysis of the 23 filled-in questionnaires revealed that three environmental factors had a particular influence; namely, temperature (41.7%), precipitation (21.1%) and RH (15.1%). Other factors, such as elevation, wind velocity, topography, soil type, vegetation, ecology and water body presence, taken together, accounted for the remaining 22.1%. The results from the second-round showed the same ranking with temperature, precipitation and RH accounting for 43.3%, 20.8% and 15.6%, respectively. Since the first three factors accounted for approximately 80% of all of the investigated environmental factors in both rounds, these three indicators were deemed of particular interest. In consideration of model parsimony, only these three environmental factors fed into the suite of models.

Risk maps produced by the biology-driven model

Three maps showing the potential risk for *P. vivax* malaria infection in P.R. China were created, employing the three most influential environmental factors. The first model took the YGDD at the 676 chosen locations into account. As can be seen in Fig. 3a, YGDD in most regions of P.R. China was higher than the 105 GDD, which is required for *P. vivax* to complete one life cycle (Deng et al., 1997). The regions with the highest YGDD are present in the south-east

with the lower ones distributed in the plateau areas.

With regard to the amount of rainfall (Fig. 3b), the potential risk decreased gradually from the south-east to north-west of the country. The dark areas represent regions with an annual precipitation exceeding 2,000 mm (e.g. Hainan, Taiwan and Guangdong), whereas the annual precipitation in Inner Mongolia, Tibet and Qinghai province is lower than 500 mm (Fig. 3b).

The third map, based on YRH, showed a gradual decrease of the RH from coastal areas towards inland. Of note, the Tibet plateau has a particular low YRH (Fig. 3c).

The overlaid final malaria map derived from three classified environmental factors by weighting predicted that *P. vivax* malaria should be mainly distributed in the south-eastern part of P.R. China with the potential risk increasing steadily from north to south (Fig. 4).

Model comparison based on statistical analysis

Based on the $wAICc$ and $wBIC$ for the suite of eight models employed (Table 1), all metrics indicated the greatest and overwhelming support for the fully saturated model, which includes all three environmental factors. However, the K-L prior used to justify AICc weighting can favour more complex models (with many tapering effects) when sample sizes are large (Link and Barker, 2006). As such, we considered BIC weighting to determine model ranking. Indeed, $wBIC$ for the fully saturated model was almost 100% of the total weight. The percentage deviance (%-DE) explained by all three environmental factors was 62.4%, suggesting the parameters used in our model produce a good level of prediction. Among the single environmental parameter models, RH had the smaller AICc and BIC values and higher %-DE compared to rainfall and YGDD.

Discussion

The frequency and transmission dynamics of mosquito-borne diseases are governed by myriad factors (MARA/ARMA, 1998; Hay et al., 2004). In the case of malaria, the disease is transmitted between

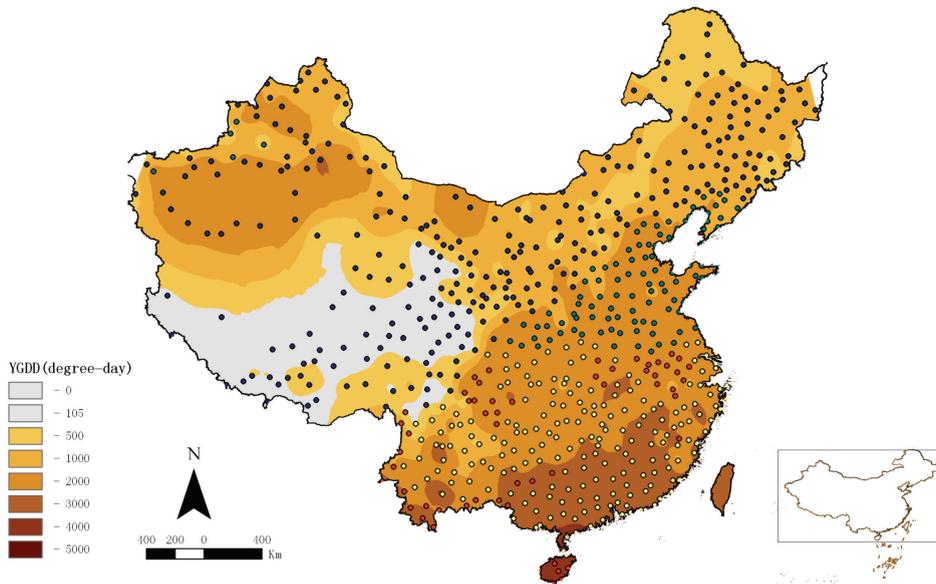


Fig. 3a. Risk map of *P. vivax* malaria in P.R. China created by yearly growing degree day (YGDD). *P. vivax* requires a 105 degree-day to complete its life cycle. Dots represent the observing stations.

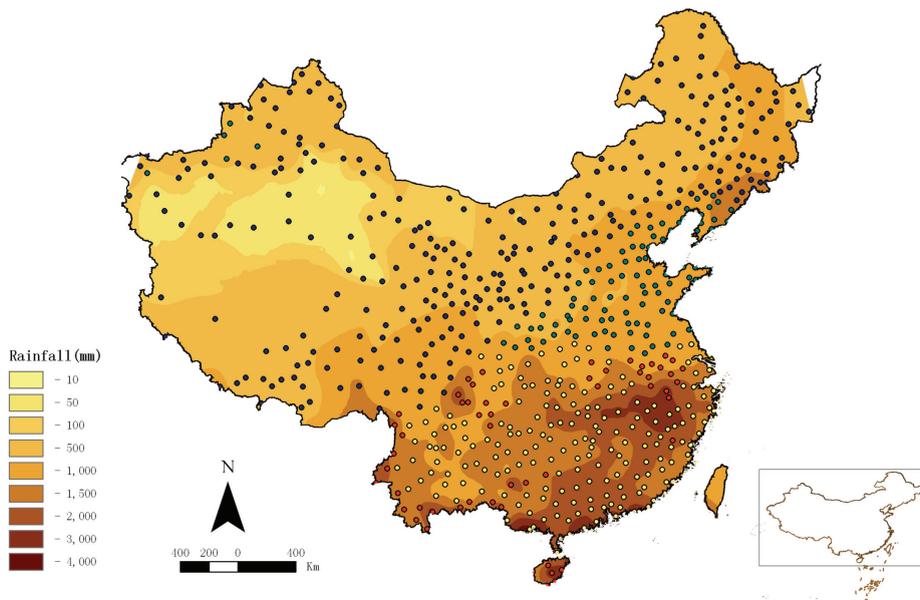


Fig. 3b. Risk map of *P. vivax* malaria in P.R. China created by rainfall. The dark areas represent regions with an annual precipitation exceeding 2,000 mm, for example Hainan, Taiwan and Guangdong provinces, whereas the annual precipitation in Inner Mongolia, Tibet and the Qinghai province is less than 500 mm. Dots represent the observing stations.

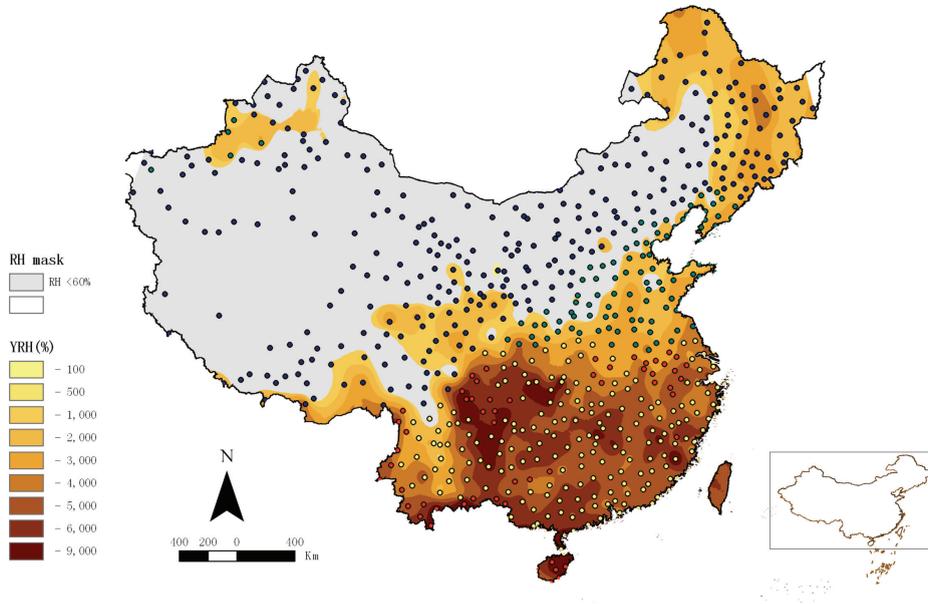


Fig. 3c. Risk map of *P. vivax* malaria in P.R. China created by effective yearly relative humidity (YRHH) masked by RH <60% showing a gradual decrease of the RH from coastal areas towards inland. Dots represent the observing stations.

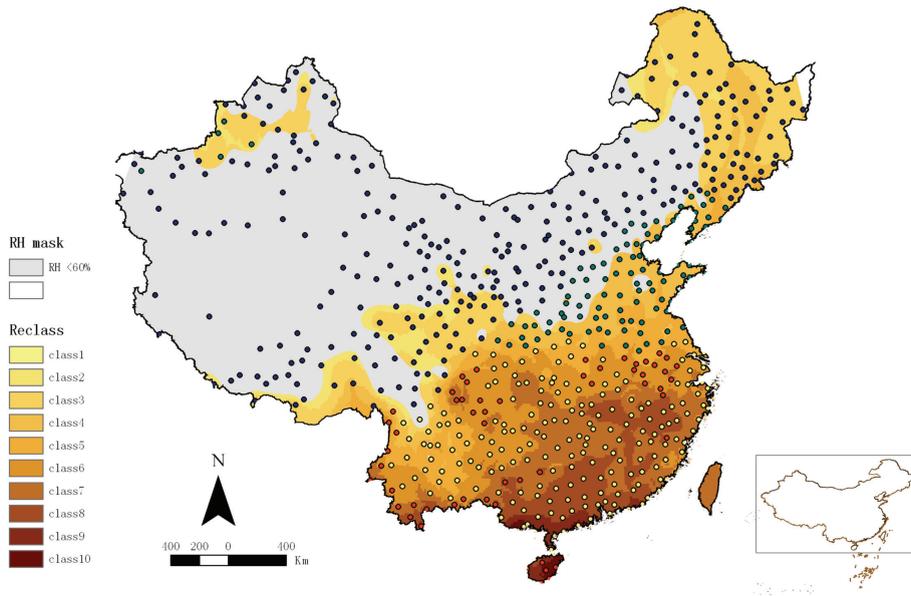


Fig. 4. Prediction of *P. vivax* malaria transmission in P.R. China by integrated modeling based on three classified environmental factors, i.e. YGDD, rainfall and YRHH, weighted as a ratio of 5:3:2, and masked by RH <60%. Dots represent the observing stations.

humans by the vector under specific environmental conditions. Our results both from a 2-step Delphi evaluation process and the regression models suggest that temperature, rainfall and RH account for approximately 80% of all the environmental factors investigated, and hence are the most important determinants for malaria transmission. This result is in agreement with the biological requirements of the parasite's life cycle. Firstly, the development of the *Plasmodium* parasite in the mosquito is primarily influenced by temperature and the survival of the parasite is strongly restricted by the threshold temperatures. Within the temperature range (from the lowest thermal threshold to the highest) at which the parasite can survive, a temperature increase is always coupled with an increase in developmental speed. Usually, temperatures below 16 °C and above 30 °C are not compatible with survival of vector and could thus restrain the development of the *Plasmodium* sporocysts in the mosquito (Deng et al., 1997). The lowest temperature *P. vivax* can sustain when developing in the *Anopheles* mosquito is 14.5 °C (Liu et al., 1998), which also explains why regions situated at elevations higher than 3,000 m above sea level are malaria-free. Secondly, although RH has no direct impact on the *Plasmodium* parasite, it still exerts an influence on transmission through the activity and life-span of the vector (Deng et al., 1997), i.e. the

lower the RH, the shorter the life-span of the vector. If the monthly average RH is lower than 60%, malaria transmission is strongly inhibited (Xu and Chen, 1989; MoH, 2007). Thirdly, rainfall has a complex impact on the transmission of malaria as it modifies the temperature and increases the RH. In addition, rainfall can also enlarge the vector habitat as mosquitoes require an aquatic environment for their larval and pupal stages (Gubler, 1998; Whelan et al., 2003). Therefore, excess rainfall can lead to malaria outbreaks, while droughts and absence of rain result in the opposite effect. However, through its other modalities, rainfall can also increase the risk of malaria (Galardo et al., 2009; Yé et al., 2009). The distribution of the rainy season can impact the fluctuation of malaria transmission in a year (Briët et al., 2008). For instance, the transmission peak of malaria in low-lying land of the temperate zone occurs after the rainy season, while it always takes place during the rainy season in the tropical forest (Craig et al., 1999; Yang et al., 2008). Once the basic knowledge of the ecology of vectors is grasped and the weak point in the life cycle identified, a strategy to control the mosquito (leading to reduction or even interruption of malaria transmission) can be formulated.

The Delphi results suggest that temperature is the most important environmental factor determining

Table 1. Suite of linear regression models employed to investigate *P. vivax* malaria-endemic situation and environmental risk factors in P.R. China.

Model	No. of parameters	AICc	wAICc	BIC	wBIC	%-DE
YRH + rain + YGDD	13	642.20	1	700.30	1	62.39
YRH + YGDD	10	698.34	0	743.13	1.00E-09	58.58
Rain + YGDD	10	727.25	0	772.03	0	56.81
Rain + YRH	10	859.23	0	904.02	0	48.75
YRH	7	930.74	0	962.16	0	44.00
Rain	7	972.22	0	1003.63	0	41.47
YGDD	7	1089.27	0	1120.69	0	34.32
1	4	1644.93	0	1662.91	0	0

Notes: yearly growing degree days (YGDD), rainfall and yearly relative humidity (YRH). The highest-ranking models are shown in boldface. Also shown are information criterion relative to models (AICc, BIC), model weights (*w*AICc, *w*BIC) and the percent deviance explained (%-DE).

P. vivax transmission in P.R. China, followed by rainfall and RH. However, according to the three single environmental factor regression models, RH is more important than rainfall and temperature (Table 1). The reason of the two sets of models resulting in different rankings can be explained as follows. Firstly, the development of *P. vivax* from larva to adult only requires 105 GDD (Deng et al., 1997), a parameter met in most of P.R. China as can be seen in the map displaying the estimated YGDD (Fig. 3a). Therefore, the key restriction for malaria transmission is the mosquito vector. Considering the fact that RH confines the distribution of the malaria vector, and no malaria transmission occurs where the monthly average RH is lower than 60% (Xu and Chen, 1989; MoH, 2007), we conjecture that the distribution of the vector, which is mainly related to the RH, determines the extent of malaria transmission. Since RH depends on rainfall patterns, it is the second most important factor in determining the abundance of the vector. Indeed, it is obvious from the maps that both RH and rainfall correspond well to the distribution of malaria transmission (Figs. 3b and 3c). However, in regions where RH is higher than 60%, temperature becomes the major driver of transmission intensity. Therefore, from the vintage point of geospatial epidemiology, the effects are different when different scales of transmission are considered.

Until now, GIS has been extensively applied when investigation of various vector-borne parasitic diseases and other diseases are strongly influenced by geographical factors (Hay et al., 2000; Bergquist, 2001; Brooker, 2002). This novel, epidemiological tool is increasingly applied in the health field and can provide guidance useful for leadership, policy-making and strategic decisions. This study investigated the three most important environmental factors which impact malaria transmission in P.R. China by applying a combination of biology-driven and statistical regression models.

A limitation of the study presented here is that not all environmental factors were taken into account for mapping and predicting the distribution of *P. vivax* malaria in P.R. China. Moreover, social and health sys-

tems factors were neglected altogether in our modeling approach. Hence, the next logical step of our analysis will focus on additional environmental factors and, most importantly, social, economic, cultural and health systems factors to further improve model specifications and predictive accuracy. Indeed, understanding social-ecological contexts and health systems are of pivotal importance to comprehend the distribution of diseases of poverty, such as malaria and the so-called neglected tropical diseases (de Savigny and Adam, 2009; Utzinger et al., 2010). Such knowledge, in turn, is crucial for spatial targeting of control interventions and, in view of the ongoing malaria elimination programme, to provide more accurate predictions and more fine-tuned assistance to surveillance and elimination (Ostrom, 2009; Reid et al., 2010).

The risk maps resulting from this study are capable of indicating the transmission intensity of malaria in various localities, as they provide superior guidance for malaria control, and hence facilitate surveillance and intervention with regard to this infection. This will be of interest for the national malaria control programme, particularly the launching of the malaria elimination project in 2010, which aims at eliminating malaria in most regions of P.R. China by 2015 and eliminating the disease in the whole country by 2020. Based on the transmission intensity map, we recommend that interventions, including vector control, swift case management within a surveillance strategy, should be focused on the meso- and hypo-endemic areas such as Hainan, Yunnan and Guangxi provinces. On the other hand, the surveillance to detect and treat all imported-cases needs to be strengthened in low-risk regions such as Shandong, Henan, Shaanxi and Gansu provinces. Clearly, the national control programme needs to shift from extensive monitoring and evaluation towards surveillance and response strategies to reach the respective elimination targets. The intensified efforts and targeted interventions undertaken in the Hainan and Yunnan provinces where the control programme, through the support of the Global Fund to Fight AIDS, Tuberculosis and Malaria since 2003, has resulted

in significant reductions of malaria transmission, now provides a positive outlook that the Chinese malaria control and elimination targets are in reach.

Acknowledgements

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