Location of active transmission sites of *Schistosoma japonicum* in lake and marshland regions in China

Z. J. ZHANG[1,2]*, T. E. CARPENTER[3], H. S. LYNN[4], Y. CHEN[5], R. BIVAND[6], A. B. CLARK[7], F. M. HUI[8], W. X. PENG[1,2], Y. B. ZHOU[1,2], G. M. ZHAO[1,2] and Q. W. JIANG[1,2]

[1] *Department of Epidemiology, School of Public Health, Fudan University, No. 138 Yi Xue Yuan Road, Shanghai 200032, China*
[2] *Key Laboratory of Public Health Safety, Fudan University, Ministry of Education, China*
[3] *Center for Animal Disease Modeling and Surveillance (CADMS), Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, One Shields Avenue, Davis, CA 95616, USA*
[4] *Department of Health Statistics, School of Public Health, Fudan University, No. 138 Yi Xue Yuan Road, Shanghai 200032, China*
[5] *Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, 451 Smyth Rd, Ottawa, Ontario, Canada*
[6] *Department of Economics, Norwegian School of Economics and Business Administration, Helleveien 3, N-5045 Bergen, Norway*
[7] *School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK*
[8] *State Key Laboratory of Remote Sensing Science, Jointly Sponsored by the Institute of Remote Sensing Applications of Chinese Academy of Sciences and Beijing Normal University, Beijing 100101, China*

SUMMARY

Schistosomiasis control in China has, in general, been very successful during the past several decades. However, the rebounding of the epidemic situation in some areas in recent years raises concerns about a sustainable control strategy of which locating active transmission sites (ATS) is a necessary first step. This study presents a systematic approach for locating schistosomiasis ATS by combining the approaches of identifying high risk regions for schisotosmiasis and extracting snail habitats. Environmental, topographical, and human behavioural factors were included in the model. Four significant high-risk regions were detected and 6 ATS were located. We used the normalized difference water index (NDWI) combined with the normalized difference vegetation index (NDVI) to extract snail habitats, and the pointwise '*P*-value surface' approach to test statistical significance of predicted disease risk. We found complicated non-linear relationships between predictors and schistosomiasis risk, which might result in serious biases if data were not properly treated. We also found that the associations were related to spatial scales, indicating that a well-designed series of studies were needed to relate the disease risk with predictors across various study scales. Our approach provides a useful tool, especially in the field of vector-borne or environment-related diseases.

Key words: *Schistosoma japonicum*, *Oncomelania hupensis*, spatial epidemiology, remote sensing, geographical information system, China.

INTRODUCTION

Schistosomiasis, a snail-transmitted trematode infection, ranks second only to malaria in the socio-economic and public health impacts in vector-borne tropical and subtropical regions (Steinmann *et al.* 2006) and is one of the most prevalent infectious diseases in the world (King *et al.* 2005). Schistosomiasis japonica, caused by *Schistosoma japonicum*, has existed in China for over 2000 years and remarkable achievements on schistosomiasis control have been made in the past 50 years (Utzinger *et al.* 2005; Zhou *et al.* 2005). But the rebound of schistosomiasis epidemic in many areas in recent years has made us reconsider the current unsustainable control strategy (Jiang *et al.* 2002; Utzinger *et al.* 2003; King *et al.* 2006).

The transmission of *S. japonicum* is closely related to the distribution of its sole intermediate host – *Oncomelania hupensis*, which is central to the control and distribution of schistosomiasis (Utzinger *et al.* 1997, 2005; Yang *et al.* 2008). Because financial support for schistosomiasis control has been reduced greatly in China (Chen, 2005), to improve the efficiency of resource allocation, high-risk places must first be identified (Beck-Wörner *et al.* 2007). Benefiting from the wide application of geographical information systems (GIS), remote sensing (RS), global positioning systems (GPS) and spatial analysis techniques (Brooker and Michael, 2000; Zhou *et al.* 2001), considerable research has been devoted to two

* Corresponding author: Department of Epidemiology, School of Public Health, Fudan University, No. 138 Yi Xue Yuan Road, Shanghai 200032, China. Tel./Fax: +86 21 54237410. E-mail: zhj_zhang@fudan.edu.cn

aspects (1) the detection of high-risk regions based on schistosomiasis cases (Raso *et al.* 2006; Rudge *et al.* 2008) and (2) the prediction of spatial distribution of potential snail habitats based on *O. hupensis* (Zhang *et al.* 2005; Yang *et al.* 2008). The former study is an essential first step to target high-risk populations in a cost-effective manner for efficient chemotherapy interventions (Beck-Wörner *et al.* 2007), but essentially serves for the unsustainable strategy of morbidity control (Singer and de Castro, 2007) which, according to previous studies, may have notable short-term control effects (Chen *et al.* 2005), but no long-term effects (Utzinger *et al.* 2003; King *et al.* 2006). However, two important limitations have not been well addressed in these studies. Non-linear relationships between the disease risk and predictors have not yet been clearly considered (Brooker *et al.* 2006; Clements *et al.* 2008) and the predicted high-risk regions might have false positive results due to the lack of statistical testing on predicted risk (Kelsall and Diggle, 1998; Zhang *et al.* 2008*a*). The latter study focused on sustainable strategy of transmission control which, however, cannot differentiate environments with infected snails from those without infected snails (Zhang *et al.* 2008*b*). Large-scale control strategies for extensive snail habitats are no longer practical, and to take long-term effective measures upon high-risk snail habitats where infected snails are present and with which people are frequently in contact (Utzinger *et al.* 1997) (referred to here as active transmission sites (ATS)), seems to be a feasible approach to eventually control or even interrupt schistosomiasis transmission. To address these issues, we used a systematic approach in this study to locate ATS in the lake and marshland regions of China based on GIS, RS, GPS and spatial statistical modelling techniques, which will help guide the local schistosomiasis control procedures.

MATERIALS AND METHODS

Study area

The study area was described in detail elsewhere (Zhang *et al.* 2008*a, b*). In brief, the area under study is Guichi region in Anhui province. It is situated in eastern China in the middle-lower reaches of the Yangtze River. From May to September, the so called 'wet season' in each year, the water from Qiupu River gradually fills up the bottomlands where the snails live; while in the 'dry season' from October to April, water in marshlands subsides completely and the grass-covered marshlands emerge again. This forms a special landscape of snail habitats – 'land in winter and water in summer' in the lake and marshland regions of China. It is the ideal environment for the survival and reproduction of *O. hupensis* and thus makes this area one of the major endemic regions of *S. japonicum* in China.

Parasitological data

A case-control study design based on the theory of spatial point process was conducted and described in detail in a previous report (Zhang *et al.* 2008*a*). Simply speaking, acute schistosomiasis cases in the study area between January 2001 and December 2006 were identified. The same number of controls was randomly chosen among the local residents to represent the spatial distribution of an underlying at-risk population that gave rise to the cases. Simultaneously, the spatial positions of the cases and controls were recorded by a hand-held global positioning system (GPS) (MobileMapper™, Thales Navigation, Inc., USA) and hence a point-based case-control spatial dataset for acute schistosomiasis was created.

Acute cases can provide more accurate information on putative exposure sites where they contact snail-infested water as compared with either chronic or advanced cases because of less recall and movement biases. For this reason, acute cases were chosen to identify high-risk regions for schistosomiasis, based on the fact that the occurrence of acute schistosomiasis is associated with the existence of high-risk habitats with infected snails (Zhang *et al.* 2008*b*).

Digitized polygon maps

Digitized polygon maps were obtained for Guichi and the Qiupu and Yangtze Rivers at a scale of 1:250 000. Then, the nearest distance of cases and controls to the Qiupu and Yangtze Rivers was calculated by using ARCGIS9.2 software (Environmental Systems Research Institute, Inc., Redlands, CA, USA).

Remote sensing images

The environmental indices used in this study were normalized difference vegetation index (NDVI) and land surface temperature (LST). Because the snail habitats are submerged in the 'wet season', RS images from dry season (October 2004) were applied to extract the above environmental variables. To minimize random errors, mean monthly values were used.

All 8-day global 1 km products for LST (5 serial images) and 16-day global 1 km products for NDVI (3 continuous images) in October 2004 that covered Guichi were processed using MODIS data and obtained from the Earth Observing System Data Gateway (http://edcimswww.cr.usgs.gov/pub/imswelcome/). The mean values for the series of composite 8-day LST and 16-day NDVI values were obtained as a measure of time-integrated stable LST and NDVI values for the cases and controls.

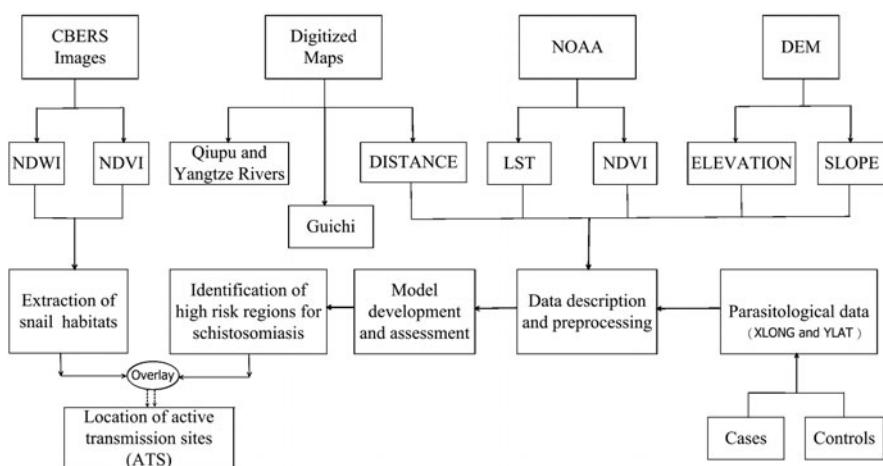In addition, to extract the snail habitats more precisely, 2 China–Brazil Earth Resources Satellite

Fig. 1. Schematic flow chart for locating active transmission sites (ATS) of schistosomiasis. It displays the general process for locating ATS by overlaying detected significant high-risk regions for schistosomiasis with spatial distribution of extracted snail habitats.

images with spatial resolution of 20 m were obtained from the China Center for Resource Satellite Data and Applications. One was on 16 October 2004, denoting the 'dry season' and another on 3 July 2005, representing the 'wet season'. Based on 2 key ecological characteristics of snail habitats, 'land in winter and water in summer' and 'no snails if no grass' (Zhou *et al.* 2001), the regions with vegetation coverage in the 'water body difference regions' for the 2 time-difference images were defined as potential snail habitats; they were obtained by extracting the 2 indices of normalized difference water index (NDWI) and NDVI, and 10 snail habitats and 10 non-snail habitats were surveyed in the field, respectively, and compared with the extracted results to evaluate the method's accuracy (see methodological details in the supplementary information – Online only).

Digital elevation model

A digital elevation model (DEM) was obtained from the interpolated DEM from the Global Land Information System of the United States Geological Survey (http://edcwww.cr.usgs.gov/landdaac/gtopo30/). Elevation and slope for cases and controls were extracted to indicate the topographic variables (Brooker and Michael, 2000).

Model development and location of ATS for schistosomiasis

There were 2 stages for the model development: extraction of the spatial distribution of snail habitats as stated above and identification of the high-risk regions for schistosomiasis using generalized additive models (GAMs) adjusted with covariates (Hastie and Tibshirani, 1990). ATS for schistosomiasis is defined as high-risk snail habitats and can thus be located by overlaying the 2 thematic layers, snail

habitats and high-risk regions of schistosomiasis. The schematic flow chart for locating the ATS of schistosomiasis is presented in Fig. 1.

In modelling schistosomiasis risk regions, the dependent variable is binary, that is whether the recorded spatial position is a case or not. The independent variables were LST and NDVI derived from RS images, elevation (ELEVATION) and slope (SLOPE) from DEM, nearest distance (DISTANCE) from the locations of cases and controls to rivers from digitized polygon maps, and the spatial coordinates of cases and controls (longitude (XLONG) and latitude (YLAT)). Preliminary data description was performed and then a table of deviance analysis for the sequential addition of each independent variable into the GAMs to test significance for the differences between models and to determine the important and significant predictors was produced. The determined important variables were then included in GAMs to predict high-risk regions of schistosomiasis. The partial residual plots were simultaneously generated to assess how well the model fitted the data and determine the possible relationships between the predictors and dependent variables. Then, the area under the receiver operating characteristic curves (AUC) was calculated to assess the overall accuracy of the model (Brooker *et al.* 2002). Finally, the risk of schistosomiasis in each position of cases and controls was calculated using the best-fitted GAMs, and the risk map for schistosomiasis was generatd by the bivariate interpolation techniques. The significance testing for the detected high-risk regions was conducted by using the approach of pointwise '*P*-value surface' (Kelsall and Diggle, 1998; Zhang *et al.* 2008*a*). The risk map of schistosomiasis, highlighting significant high-risk regions with 95% contour lines, was then overlaid with the extracted snail habitats and our previous clustering analysis results, using relative risk surface, excess risk surface and spatial scan

Table 1. *Summary of the predictors for developing a model to detect high-risk regions of schistosomiasis*

| Variables* | Unit | Indices | | | |
		Min.	Max.	Median	Quartile Range
LST	Kelvin	295·60	301·10	298·40	1·20
NDVI	—	0·33	0·81	0·60	0·17
SLOPE	Degree	0·06	12·68	0·66	1·14
ELEVATION	Meter	0·00	257·00	33·50	48·00
DISTANCE	Meter	26·20	38838·50	3906·70	10270·70
XLONG	Meter	519212·00	576734·00	543089·00	23194·00
YLAT	Meter	3355173·00	3408742·00	3385905·00	22042·00

* LST: land surface temperature; SLOPE: slope in the locations of cases and controls; NDVI: normalized difference vegetation index; ELEVATION: altitude in the locations of cases and controls above sea level; DISTANCE: nearest distance from the locations of cases and controls to the Qiupu and Yangtze Rivers; XLONG: x-axis coordinates after projection; YLAT: y-axis coordinates after projection.

statistic approaches to locate ATS of schistoso-miasis and explore advantages of GAMs, respectively (Zhang *et al.* 2008*a*). The statistical analsyis was performed using R2.7.1 software (R Development Core Team, Vienna, Austria).

For the detection of ATS of schistosomiasis, we obtained the range of their spatial coordinates in ARCGIS9.2 software (Environmental Systems Research Institute, Inc., Redlands, CA, USA), and then found these locations through the navigation of the hand-held GPS settings (MobileMapper™, Thales Navigation, Inc., USA) to validate, using historical surveillance data from the local area, and carry out a field survey on infected snails.

RESULTS

Data description

In total, 83 spatial locations for cases and 83 for controls were obtained. The map of their spatial distribution was presented previously (Zhang *et al.* 2008*a*).

The predictors are summarized in Table 1. The two environmental factors of LST and NDVI and the topographical factor of SLOPE varied slightly; while other variables showed large variations, suggesting that *O. hupensis* can only breed and live in certain suitable microenvironments (Zhang *et al.* 2005), and that the variables with large variations may have greater impacts on snail survival and schistosomiasis risk. To reduce data variation and possible impacts of extreme values, Box-Cox transformation was applied to the covariates, and transformed variables were used in the modelling process.

Fitting GAMs to delineate high-risk regions for schistosomiasis

Deviance analysis for the sequential addition of each independent variable into GAMs is displayed in

Table 2. DISTANCE was the most important variable because of the smallest deviance (models 1–8), and statistical significance was further found for LST, ELEVATION, XLONG and YLAT, even DISTANCE remained in the GAMs (models 9–14). LST became insignificant and was excluded from the final GAMs because it became nonsignificant when the other four variables were simultaneously included.

The partial fits of the final GAMs to estimate the 'smoothed' relationships with each predictor are displayed in Fig. 2. ELEVATION showed a quadratic relationship to the risk of schistosomiasis, which tended to decrease when ELEVATION was larger than about 9 (original value was about 86 m). DISTANCE was a piecewise linear function. When DISTANCE was less than about 14 (original value was about 1500 m), the schistosomiasis risk was initially very high. The risk decreased very slowly as DISTANCE increased; while the risk decreased rapidly to a stable low risk when DISTANCE was between 14 (original value is about 1500 m) and 24 (original value is about 18 000 m). This may suggest that local residents may have a consistently high risk of schistosomiasis within 1500 m of the risk environments, and low risk beyond 18 000 m. Spatial locations were also significant predictors and showed different impacts for forecasting the risk of schisto-somiasis, linear and approximate positive relationship for XLONG and piecewise linear and roughly negative functions for YLAT.

ROC curves for the above fitted GAMs were generated to evaluate the model accuracy of discrimination and its AUC was 0·911, indicating a very good prediction capacity.

Four significant high-risk regions for schistoso-miasis were detected using the method of '*P*-value surface'. The overlaid map for the interpolated risk map of schistosomiasis with significant risk regions highlighted and the previous results from relative risk surface, excess risk surface and spatial scan

Table 2. *Deviance analysis to determine the important variables for developing GAMs*

Model	Term	Degree of freedom	Deviance	P value*
1	Constant	—	230·12	—
2	S(LST)	1	229·85	0·601
3	S(SLOPE)	1	224·01	0·013
4	S(NDVI)	1	225·27	0·028
5	S(ELEVATION)	1	228·82	0·253
6	S(DISTANCE)	1	214·27	<0·001
7	S(XLONG)	1	229·24	0·345
8	S(YLAT)	1	229·41	0·399
9	S(DISTANCE)+S(LST)	4	11·286	0·024
10	S(DISTANCE)+S(SLOPE)	4	5·147	0·273
11	S(DISTANCE)+S(NDVI)	4	3·21	0·523
12	S(DISTANCE)+S(ELEVATION)	4	20·001	<0·001
13	S(DISTANCE)+S(XLONG)	12	20·435	0·060
14	S(DISTANCE)+S(YLAT)	9	24·091	0·004

* Models 2–8 were compared with model 1 and models 9–14 were compared to model 6 to get the *P* values, which were obtained by Chi-square test; XLONG and YLAT are spatial coordinates of cases and controls, and they would be included in the model simultaneously only if one of them was significant for predicting the risk of schistosomiasis because a location could not be determined by either a single XLONG or only YLAT.
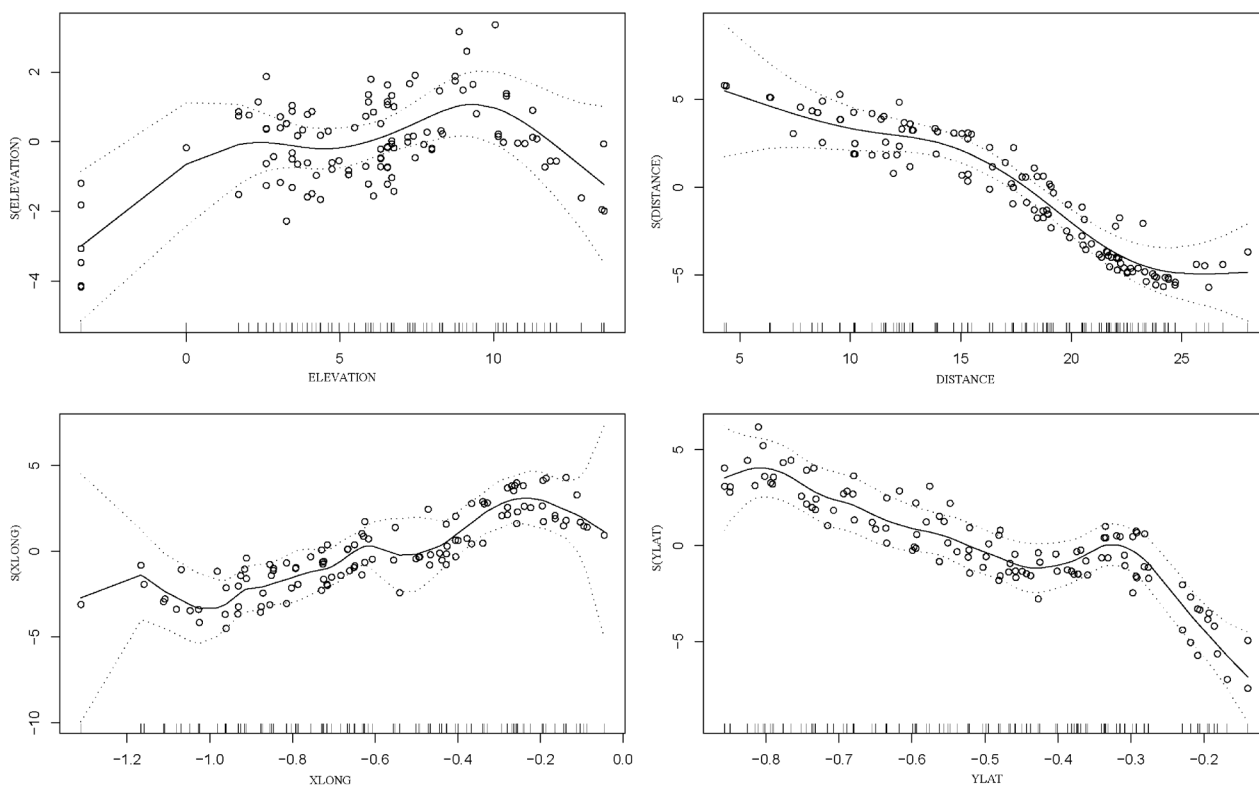

Fig. 2. Partial fits of GAMs to estimate the 'smoothed' relationships with the four predictors of ELEVATION, DISTANCE, XLONG and YLAT. The separate circles denote partial residuals of each term, the solid curve is the fit for each term, and the dotted curves are pointwise standard error curves.

statistic approaches are displayed in Fig. 3A. From the 2 common significant high-risk regions in the north and southeast of Guichi, the GAMs approach identified high-risk regions of schistosomiasis more precisely, which helps to locate ATS. Two additional significant high-risk regions were detected in the northeast and south by using GAMs.

Snail habitats and ATS for schistosomiasis

Fig. 3B (enlarged in C, D, E, and F) shows the GAMs-identified ATS relative to the extracted snail habitats in Guichi using RS images. The approach to extract snail habitats shows good accuracy with a sensitivity of 90% and specificity of 100% (see
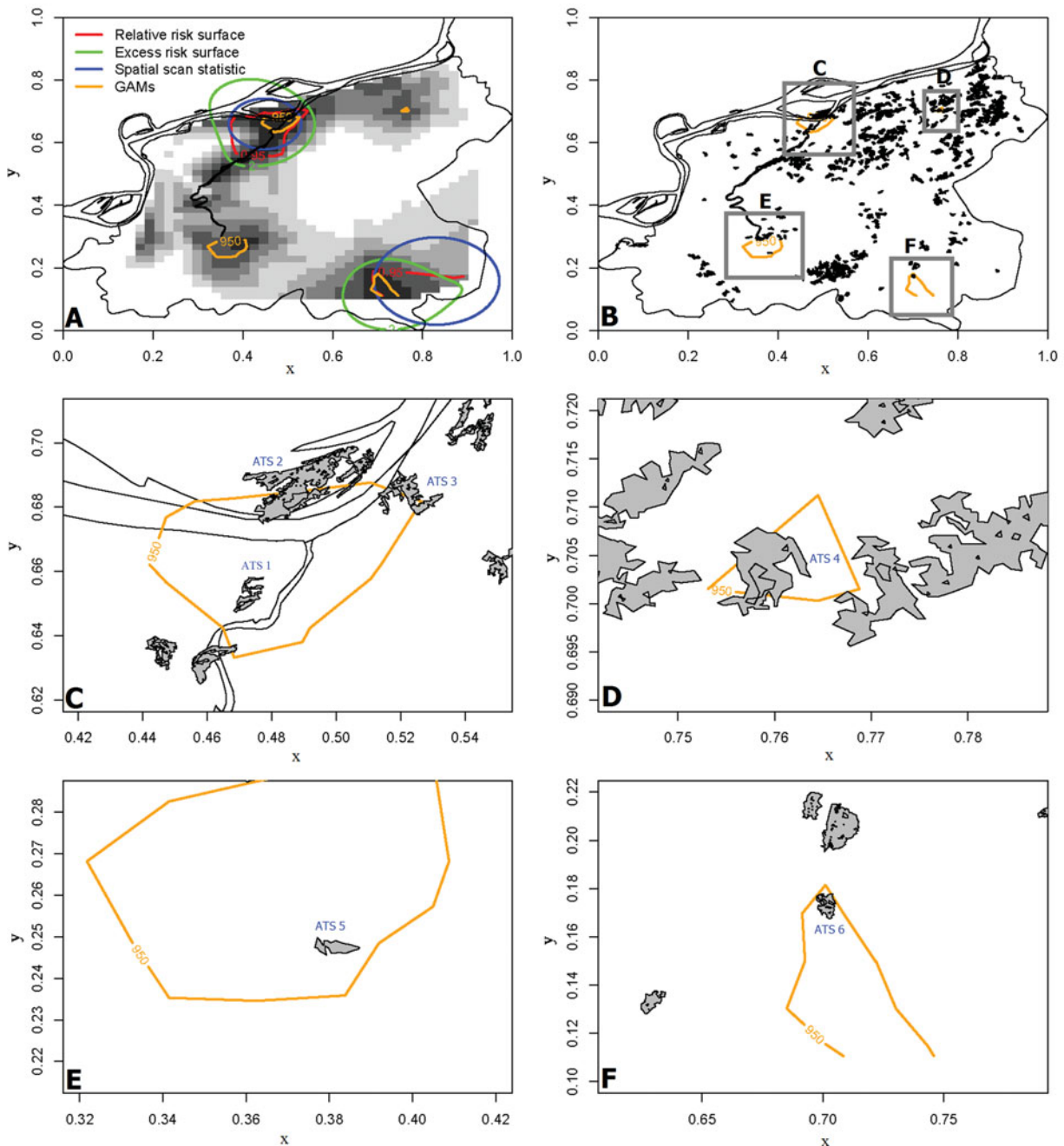
Fig. 3. Location of active transmission sites (ATS) using GAMs results in detection of significant high-risk regions of schistosomiasis, relative risk surface, excess risk-surface and spatial-scan statistic results. (To preserve confidentiality, the figures were created by re-scaling the coordinates into intervals [0, 1]). (A) Results from GAMs, relative risk surface, excess risk-surface and spatial-scan statistic approaches. (B) Overlaid are the four significant risk regions detected by GAMs with extracted snail habitats to locate ATS. The area for the snail habitats is extensive and several snail habitats were indeed located within these risk regions, see (C, D, E, and F) for enlarged maps.

supplementary information – Online only). There are 349 places with snail habitats with an overall area of about 107 km². The area for snail habitats is extensive and hence long-term effective control strategies for schistosomiasis may only be possible in the specific high-risk regions, identified here as ATS, which had a combined area of about 2·32 km², confirmed by field investigations because infected snails and acute schistosomiasis cases were found there at all times (results available upon request).

DISCUSSION

Following the implementation of a 10-year World Bank Load Project, China has successfully reduced schistosomiasis-specific morbidity (Chen *et al.* 2005); however, re-emergence of the epidemic indicates that maintaining and consolidating the achievements obtained remains a great challenge. It has been suggested that the control strategy of schistosomiasis should be changed from morbidity

control to transmission control with finite and focused snail control as an emphasis for long-term sustainable control effects (Singer and de Castro, 2007). To do this, the ATS must first be located. In the past, several approaches were used to identify ATS, such as field surveys of snails (Sturrock, 1986), cercariometry (Aoki *et al*. 2003) and sentinel mice approaches (Li *et al*. 2000*a*; Wang *et al*. 2009). Collection and examination of snails in the field requires considerable manpower and some areas are difficult to access, especially during floods (Guo *et al*. 2005; Li *et al*. 2000*a*). False negative results frequently occur because of the current low density of infected snails in China. Low sensitivity was also found for the cercariometry method (Muhoho *et al*. 1997). As for sentinel mice approach, it is expensive and takes a long time to obtain the results (Li *et al*. 2000*a*). Relatively inexpensive and rapid methods to identify ATS need to be developed. In this study, we suggested a systematic and feasible approach to locate ATS for schistosomiasis at a small scale to support decision making for the local governors, whose work will directly determine the ultimate effects of schistosomiasis control (Li *et al*. 2000*b*). The combination of this method and the identification of populations and regions at high risk will provide a two-step integrated procedure for better decision making on schistosomiasis control.

It is well recognized that the life cycle of *S. japonicum* is complicated, and geographical, environmental, social and economic factors determine its focal endemicity (Guo *et al*. 2005; Zhou *et al*. 2001). To account for this, we considered the related environmental (NDVI and LST), topographic (ELEVATION and SLOPE), social behavioural factors (DISTANCE) and geographical locations (XLONG and YLAT) to detect high-risk regions of schistosomiasis based on the theories of the point-based random process, overlaid with the extracted snail habitats to locate ATS. This will facilitate the allocation of limited resources and the carrying out of routine work more efficiently in the local region. This approach extends a previous study (Zhang *et al*. 2008*a*), which focused on the theoretical development of the point process and did not adjust for covariates. The area-based approaches to identify high-risk regions were not appropriate here and the reasons for this have been explained elsewhere (Zhang *et al*. 2008*a,b*).

In this study, we found that environmental factors (LST and NDVI) had little variation, and did not significantly predict the risk of schistosomiasis. The reasons may be that their effects have been replaced by ELEVATION and DISTANCE in small-scale studies because close correlations existed between them (Zhang *et al*. 2008*c*). The topographical factors (ELEVATION and SLOPE) were more important than environmental factors. ELEVATION had a statistically significant quadratic relationship with

the risk of schistosomiasis, while SLOPE was not significant at small scale, although it is important in larger-scale studies (Brooker and Michael, 2000; Beck-Wörner *et al*. 2007). DISTANCE was regarded as an indicator of human behaviour for contacting snail-infested water, and was found to be the most important factor for schistosomiasis. This result was consistent with those from other studies (Rudge *et al*. 2008). DISTANCE shows a piecewise linear function in the final GAMs with inflexions for the risk regions at about 1500 m and 18 000 m. The high-risk regions of schistosomiasis are within 1500 m of the risk environments, which is consistent with previous studies analysed by other methods (e.g. buffer-zone analyses) (Chen and Lin, 2004; Hu *et al*. 2007). More than that, a new inflection for low-risk regions was found, which suggests that the regions with a DISTANCE $\geqslant$18 000 m away from the risk environments were at a low and stable risk for schistosomiasis. Our results indicate that at small scale, the important risk factors for schistosomiasis are human behaviour, geographical factors, and then environmental factors in that order, which implies that health education aimed at strengthening the consciousness of populations at risk for schistosomiasis control and improving their capability for self-protection against schistosomiasis may be an important and effective measure in the endemic regions of schistosomiasis (Hu *et al*. 2005).

Significant risk factors for schistosomiasis identified in this study are not entirely consistent with those reported in previous studies, which may be due to the following reasons. First, the study scale is different, for which risk factors may have different impacts (Zhang *et al*. 2008*c*). Another reason for the inconsistency may be the non-linear relationships between the predictors and schistosomiasis risk, which were displayed by the partial residual plots of GAMs and ignored or not adequately addressed in previous studies (Raso *et al*. 2006). For a simple comparison, we fitted a parametric linear model without considering the possible non-linear relationships. The difference is significant between it and GAMs (Deviance $= -72\cdot62$, P $=1\cdot544$e-06) and its AUC is $0\cdot727$. It has a worse discriminative capacity compared with GAMs, and the masked non-linear relationships would cause a serious bias for estimation (detailed results available upon request and not displayed here).

The risk map for schistosomiasis from GAMs is in essence a point estimate of risk without statistical testing. In order to avoid over-interpretating the reults, statistical tests for the predicted disease risk need to be conducted. Here, we refer to the idea of the piecewise '*P*-value surface' (Kelsall and Diggle, 1998), which was first applied in schistosomiasis studies by Zhang *et al*. (2008*a*). We obtained the significant risk regions with 95% contour lines delineated, and compared them with previous results of

clustering analysis (Zhang *et al*. 2008 *a*). The GAMs approach with piecewise '*P*-value surface' is better than relative risk surface, excess risk surface and spatial scan statistic methods, possibly because additional covariates were included (Webster *et al*. 2006). Relative risk and excess risk surfaces cannot take the information of covariates into account (Zhang *et al*. 2008 *a*). The spatial scan statistic approach can only include binary covariates into the models, so part of the information may be lost (Kulldorff, 2006). In Fig. 3A, GAMs identified the same two high-risk regions as previous results, but the position is more precise. And it also detected 2 additional significant risk regions, which were not identified by the other 3 cluster analysis approaches. In addition, we need also to know the spatial distributions of snail habitats to locate ATS for schistosomiasis. In order to extract snail habitats more accurately, we combined NDWI and NDVI indices based on 2 key ecological characteristics of snail habitats. NDVI has been widely and successfully used to extract snail habitats (Guo *et al*. 2005; Yang *et al*. 2005; Zhang *et al*. 2005), but the single application of NDVI will result in considerable misclassification of snail-free areas in rice agro-ecosystems, and confound with other vegetation types unrelated with snail habitats (Guo *et al*. 2005). NDWI was used here to reduce these errors for the first time. Finally, 6 ATS for schistosomiasis were located by overlaying significant high-risk regions with extracted snail habitats. The ranges of 1500 m surrounding the ATS are the emphasis for current schistosomiasis control in Guichi. The long-term effective measures for these sites should be explored and performed to compress the high-risk regions for schistosomiasis and ultimately interrupt schistosomiasis transmission.

In conclusion, this study presents a systematic approach to identifying the location of ATS, focusing on a small-scale study by joining the detection of high-risk regions of schistosomiasis and the extraction of snail habitats. Two findings might be important for future studies. One was that we found complicated non-linear relationships between predictors and the risk of schistosomiasis, which cannot be easily captured by simple linear parametric models that were widely used in previous studies. We also found that variables associated with schistosomiasis might have different predictability for the risk of schistosomiasis at different study scales. Therefore, a well-designed series of studies is needed to relate the risk of schistosomiasis with predictors across various spatial scales, and the inherent spatial heterogeneity of disease risk at different scales needs to be further explored. We are confident that the approaches presented in this study may also be used in other vector-borne or environment-related diseases where there are complex relationships between exposure and disease outcome.

REFERENCES

Aoki, Y., Sato, K., Muhoho, N. D., Noda, S. and Kimura, E. (2003). Cercariometry for detection of transmission sites for schistosomiasis. *Parasitology International* **52**, 403–408.

Beck-Wörner, C., Raso, G., Vounatsou, P., N'Goran, E. K., Rigo, G., Parlow, E. and Utzinger, J. (2007). Bayesian spatial risk prediction of schistosoma mansoni infection in western Cote d'Ivoire using a remotely-sensed digital elevation model. *American Journal of Tropical Medicine and Hygiene* **76**, 956–963.

Brooker, S. and Michael, E. (2000). The potential of geographical information systems and remote sensing in the epidemiology and control of human helminth infections. *Advances in Parasitology* **47**, 245–288.

Brooker, S., Hay, S. I. and Bundy, D. A. (2002). Tools from ecology: useful for evaluating infection risk models? *Trends in Parasitology* **18**, 70–74.

Brooker, S., Clements, A. C., Bundy, D. A. P. (2006). Global epidemiology, ecology and control of soil-transmitted helminth infections. *Advances in Parasitology* **62**, 221–261.

Chen, H. G. and Lin, D. D. (2004). The prevalence and control of schistosomiasis in Poyang Lake region, China. *Parasitology International* **53**, 115–125.

Chen, X. Y. (2005). Schistosomiasis control strategy, administrative pattern, financial support and technological processes under different background in China. Ph.D. thesis, Fudan University, China.

Chen, X. Y., Wang, L. Y., Cai, J. M., Zhou, X. N., Zheng, J., Guo, J. G., Wu, X. H., Engels, D. and Chen, M. G. (2005). Schistosomiais control in China: the impact of a 10-year World Bank Loan Project (1992–2001). *Bulletin of the World Health Organization* **83**, 43–48.

Clements, A. C., Brooker, S., Nyandindi, U., Fenwick, A. and Blair, L. (2008). Bayesian spatial analysis of a national urinary schistosomiasis questionnaire to assist geographic targeting of schistosomiasis control in Tanzania, East Africa. *International Journal for Parasitology* **38**, 401–415.

Guo, J. G., Vounatsou, P., Cao, C. L., Utzinger, J., Zhu, H. Q., Anderegg, D., Zhu, R., He, Z. Y., Li, D., Hu, F., Chen, M. G. and Tanner, M. (2005). A geographic information and remote sensing based model for prediction of *Oncomelania hupensis* habitats in the Poyang Lake area, China. *Acta Tropica* **96**, 213–222.

Hastie, T. and Tibshirani, R. (1990). *Generalized Additive Models*. Chapman and Hall, London, UK.

Hu, F., Lin, D. D., Liu, Y., Liu, Y. M., Huang, X. H., Gao, B., Li, Z. S., Li, J. Y. and Gao, Z. L. (2007). Studies on relationship between spatial distribution of people's behavior and infection of *Schistosoma japonicum* in Poyang Lake region. *Chinese Journal of Schistosomiasis Control* **19**, 345–348.

Hu, G. H., Hu, J., Song, K. Y., Lin, D. D., Zhang, J., Cao, C. L., Xu, J., Li, D. and Jiang, W. S. (2005). The role of health education and health promotion in the control of schistosomiasis: experiences from a 12-year intervention study in the Poyang Lake area. *Acta Tropica* **96**, 232–241.

Jiang, Q. W., Wang, L. Y., Guo, J. G., Chen, M. G., Zhou, X. N. and Engels, D. (2002). Morbidity control of schistosomiasis in China. *Acta Tropica* **82**, 115–125.

Kelsall, J. E. and Diggle, P. J. (1998). Spatial variation in risk of disease: a nonparametric binary regression approach. *Applied Statistics* **47**, 559–573.

King, C. H., Dickman, K. and Tisch, D. J. (2005). Reassessment of the cost of chronic helmintic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. *Lancet* **365**, 1561–1569.

King, C. H., Sturrock, R. F., Kariuki, H. C. and Hamburger, J. (2006). Transmission control for schistosomiasis – why it matters now. *Trends in Parasitology* **22**, 575–582.

Kulldorff, M. (2006). *SaTScan^{TM} User Guide for Version 7.0*. http://www.satscan.org/

Li, Y. S., Sleigh, A. C., Williams, G. M., Ross, A. G. P., Li, Y., Forsyth, S. J., Tanner, M. and McManus, D. P. (2000*a*). Measuring exposure to *Schistosoma japonicum* in China. III. Activity diaries, snail and human infection, transmission ecology and options for control. *Acta Tropica* **75**, 279–289.

Li, Y. S., Sleigh, A. C., Ross, A. G. P., Williams, G. M., Tanner, M. and McManus, D. P. (2000*b*). Epidemiology of *Schistosoma japonicum* in China: morbidity and strategies for control in the Dongting Lake region. *International Journal for Parasitology* **30**, 273–281.

Muhoho, N. D., Katsumata, T., Kimura, E., Migwi, D. K., Mutua, W. R., Kiliku, F. M., Habe, S. and Aoki, Y. (1997). Cercarial density in the river of an endemic area of schistosomiasis haematobia in Kenya. *American Journal of Tropical Medicine and Hygiene* **57**, 162–167.

Raso, G., Vounatsou, P., Singer, B. H., N'Goran, E. K., Tanner, M. and Utzinger, J. (2006). An integrated approach for risk profiling and spatial prediction of *Schistosoma mansoni*-hookworm coinfection. *Proceedings of the National Academy of Sciences, USA* **103**, 6934–6939.

Rudge, J. W., Stothard, J. R., Basanez, M. G., Mgeni, A. F., Khamis, I. S., Khamis, A. N. and Rollinson, D. (2008). Micro-epidemiology of urinary schistosomiasis in Zanzibar: Local risk factors associated with distribution of infections among schoolchildren and relevance for control. *Acta Tropica* **105**, 45–54.

Singer, B. H. and de Castro, M. C. (2007). Bridges to sustainable tropical health. *Proceedings of the National Academy of Sciences, USA* **104**, 16038–16043.

Steinmann, P., Keiser, J., Bos, R., Tanner, M. and Utzinger, J. (2006). Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *The Lancet Infectious Diseases* **6**, 411–425.

Sturrock, R. F. (1986). Snail collection to detect schistosome transmission sites. *Parasitology Today* **2**, 59–61.

Utzinger, J., Mayombana, C., Mez, K. and Tanner, M. (1997). Evaluation of chemical and physical-morphological factors as potential determinants of *Biomphalaria pfeifferi* (Krauss, 1848) distribution. *Memórias do Instituto Oswaldo Cruz* **92**, 323–328.

Utzinger, J., Bergquist, R., Xiao, S. H., Singer, B. H. and Tanner, M. (2003). Sustainable schistosomiasis control – the way forward. *Lancet* **362**, 1932–1934.

Utzinger, J., Zhou, X. N., Chen, M. G. and Bergquist, R. (2005). Conquering schistosomiasis in China: the long march. *Acta Tropica* **96**, 69–96.

Wang, L. D., Chen, H. G., Guo, J. G., Zeng, X. J., Hong, X. L., Xiong, J. J., Wu, X. H., Wang, X. H., Wang, L. Y., Xia, G., Hao, Y., Chin, D. P. and Zhou, X. N. (2009). A strategy to control transmission of *Schistosoma japonicum* in China. *The New England Journal of Medicine* **360**, 121–128.

Webster, T., Vieira, V., Weinberg, J. and Aschengrau, A. (2006). Method for mapping population-based case-control studies: an application using generalized additive models. *International Journal of Health Geographics* **5**, 26. Doi: 10.1186/1476-072X-5-26.

Yang, G. J., Vounatsou, P., Zhou, X. N., Tanner, M. and Utzinger, J. (2005). A Bayesian-based approach for spatio-temporal modeling of county level prevalence of *Schistosoma japonicum* infection in Jiangsu province, China. *International Journal for Parasitology* **35**, 155–162.

Yang, K., Wang, X. H., Yang, G. J., Wu, X. H., Qi, Y. L., Li, H. J. and Zhou, X. N. (2008). An integrated approach to identify distribution of *Oncomelania hupensis*, the intermediate host of *Schistosoma japonicum*, in a mountainous region in China. *International Journal for Parasitology* **38**, 1007–1016.

Zhang, Z. J., Clark, A. B., Bivand, R., Chen, Y., Carpenter, T. E., Peng, W. X., Zhou, Y. B., Zhao, G. M. and Jiang, Q. W. (2008*a*). Nonparametric spatial analysis to detect high risk regions for schistosomiasis in Guichi, China. *Transactions of the Royal Society of Tropical Medicine and Hygiene* (in the Press). doi:10.1016/j.trstmh.2008.11.012

Zhang, Z. J., Carpenter, T. E., Chen, Y., Clark, A. B., Lynn, H. S., Peng, W. X., Zhou, Y. B., Zhao, G. M. and Jiang, Q. W. (2008*b*). Identifying high-risk regions for schistosomiasis in Guichi, China: A spatial analysis. *Acta Tropica* **107**, 217–223.

Zhang, Z. J., Ong, S. H., Peng, W. X., Zhou, Y. B., Zhuang, J. L., Zhao, G. M. and Jiang, Q. W. (2008*c*). A model for the prediction of *Oncomelania hupensis* in the lake and marshland regions, China. *Parasitology International* **57**, 121–131.

Zhang, Z. Y., Xu, D. Z., Zhou, X. N., Zhou, Y. and Liu, S. J. (2005). Remote sensing and spatial statistical analysis to predict the distribution of *Oncomelania hupensis* in the marshlands of China. *Acta Tropica* **96**, 205–212.

Zhou, X. N., Malone, J. B., Kristensen, T. K. and Bergquist, N. R. (2001). Application of geographic information systems and remote sensing to schistosomiasis control in China. *Acta Tropica* **79**, 97–106.

Zhou, X. N., Wang, L. Y., Chen, M. G., Wu, X. H., Jiang, Q. W., Chen, X. Y., Zheng, J. and Utzinger, J. (2005). The public health significance and control of schistosomiasis in China – then and now. *Acta Tropica* **96**, 97–105.