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Eco-social determinants of *Schistosoma japonicum* infection supported by multi-level modelling in Eryuan County, People's Republic of China

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ABSTRACT

Schistosomiasis remains of considerable public health concern in many tropical and subtropical regions of the world, including the People's Republic of China. The effectiveness of schistosomiasis control interventions are, among other factors, governed by the social-ecological context. However, eco-social determinants of schistosomiasis are poorly understood, particularly at the household or village levels. In the current study, residents in 26 villages of Eryuan county, Yunnan Province, People's Republic of China, were screened for *Schistosoma japonicum* infection with a serological assay that was followed by stool examination for sero-positive individuals. Bayesian multilevel models with spatial random effects were employed to profile the *S. japonicum* infection risk based on known transmission sites of *S. japonicum* that are scattered across individual land parcels in this part of the country. The key risk factors identified with this approach were the absence of a sanitary stall house for livestock and presence of living and infected intermediate host snails in close proximity. We conclude that a spatially explicit Bayesian multilevel approach can deepen our understanding of eco-social determinants that govern schistosomiasis transmission at a small geographical scale.

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1. Introduction

The transmission of schistosomiasis, a water-associated disease, is governed by behavioural, cultural, demographic, ecological, economic, social and intrinsic host factors (Cotruvo et al., 2004). The effectiveness of interventions, therefore, depends on the local social-ecological systems (Morens et al., 2004; Wilson, 1995). The eco-social determinants in the local environment can be modelled mathematically, which holds promise to deepen our understanding of the frequency and transmission dynamics of schistosomiasis (Fenwick, 2006; Spear et al., 2006). Of note, the incorporation of

social and ecological variables into epidemiological models as a tool for anticipating and assessing impacts of environmental transformations and social change has been done before (Codeco et al., 2008; Krieger, 2001).

Schistosomiasis japonica is an important parasitic disease in the People's Republic of China (PR China). The intermediate host, the amphibious snail *Oncomelania hupensis* is mainly distributed along the Yangtze River valley and in southern PR China (Fan, 2012; Zhou et al., 2005, 2007a). Snails are infected by miracidia, the larval stage of *S. japonicum* that hatch from eggs deposited in faeces of mammalian definitive hosts which include humans, bovines and other domestic and wild animal species. The infected snails release cercariae into the water (Hong et al., 2013; Liang and Spear, 2008; Wilke et al., 2000). The definitive hosts are infected by cercariae that penetrate the skin; in the case of humans most often during water-related activities, such as fishing, cultivating crops, cutting weeds, washing clothes and swimming. Interventions to control the

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morbidity due to schistosomiasis emphasise periodic treatment of at-risk populations with the drug praziquantel, while transmission control and eventual elimination focus on interrupting the life cycle of the parasite. To be successful, particular consideration should be given to key eco-social risk factors (Utzing et al., 2005; Zhou et al., 2013). For example, a methane gas pit can be designed for collection of human excreta, so that *S. japonicum* eggs released by human faeces are trapped, and hence environmental contamination with *S. japonicum* eggs is reduced or interrupted (Zeng et al., 2008).

Although great progress has been achieved in the control and local elimination of schistosomiasis japonica in PR China through the implementation – for over half a century – of a national schistosomiasis control programme, approximately 65 million individuals are still at risk of infection (Utzing et al., 2005; Zhou et al., 2005). Meanwhile, changes in transmission patterns due to demographic and ecological transformations (e.g. major water resources development and management projects), health systems reforms and uneven socio-economic development, have resulted in changing patterns of schistosomiasis transmission (Utzing et al., 2005; Zhou et al., 2005). Moreover, data from the latest national survey suggest that schistosomiasis transmission has re-emerged in 38 counties across the seven provinces where the disease remains endemic (Zhou et al., 2005, 2007a). It has been argued that environmental, programmatic and socio-economic factors played a role in this re-emergence (Liang et al., 2006, 2007; Zhou et al., 2008). Our previous studies revealed that risk factors for human infections with *S. japonicum* occur at individual, household and village levels (Jia et al., 2007; Lv et al., 2013; Steinmann et al., 2007b; Yang et al., 2005). There is a growing body of literature showing that multilevel modelling is a suitable approach to account for such a hierarchical structure of eco-social factors at the community level (Diez-Roux, 2000; Ferrari et al., 2008; Shor et al., 2007; Zhu et al., 2006).

The purpose of this study was to deepen the understanding of eco-social determinants of *S. japonicum* infection in humans. An important justification for this study is that the recently adopted comprehensive strategy to block transmission of *S. japonicum* in the lake and marshland regions of PR China cannot easily be adapted to distinct ecosystems of the hilly and mountainous region (Liang et al., 2006; Wang et al., 2009; Yang et al., 2008). For instance, the transmission sites of *S. japonicum* are scattered across individual land parcels in the hilly and mountainous regions (Yang et al., 2008, 2009) requiring that specific control measures be applied to small patches of land within the mountainous area, which fundamentally differs from what is proposed for the lake and marshland regions (Liu et al., 2013; Wang et al., 2006). Hence, the current study aimed at the identification of specific eco-social determinants of schistosomiasis japonica transmission at the community level in the hilly and mountainous regions of PR China in order to assist with the design of a control strategy adapted to the local level. We focused on eco-social determinants of schistosomiasis transmission, and the potential of informed interventions for altering the outcomes that are governed by these risk factors.

2. Materials and methods

2.1. Ethics statement

The study was approved by the institutional review boards of the National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention (Shanghai, PR China) and the Jiangsu Institute of Parasitic Diseases (Wuxi, PR China). Written informed consent was obtained from the heads of participating households or designated literate substitutes.

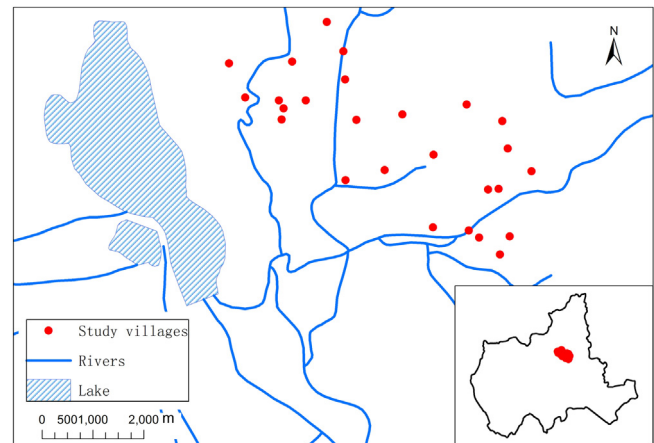


Fig. 1. Location of the 26 study villages in Eryuan county, Yunnan province, south-western PR China.

2.2. Study area and population

The study was carried out in 26 villages in the schistosomiasis japonica-endemic hilly and mountainous region of eastern Eryuan county, Yunnan Province (Fig. 1). Cibihi Lake, the largest freshwater body in the region, is located in the western part of the study area. In 2005/2006, the prevalence of *S. japonicum* infection in humans was about 2.7% in this region (Steinmann et al., 2007a).

Our study was implemented between March and June 2007. Based on the national specifications for schistosomiasis control, an exhaustive sampling was pursued. In short, more than 90% of the households in the study villages were selected from readily available community registries (Hong et al., 2011; Zhou et al., 2011). More than 90% of all household members aged ≥ 6 years were invited to participate in the study.

2.3. Cross-sectional parasitological and questionnaire survey

A venous blood sample was collected from each participant and subsequently subjected to an indirect haemagglutination (IHA) test for IgG antibodies against *S. japonicum* (test provided by Anhui Institute of Parasitic Diseases; Hefei, PR China) (Jia et al., 2009). Further, a stool sample was collected from sero-positive individuals and analysed for *S. japonicum* infection using a miracidium hatching test (Li et al., 2003). All participants with a positive serological test were treated with praziquantel following national guidelines.

Demographic variables (i.e. name, age and sex) were obtained from readily available village registries and checked during the blood and stool sample collection. A household-level questionnaire was administered to all heads of households to obtain the following information: economic and living conditions (e.g. size of farmland, number of livestock, water supply and income resources), livestock breeding information, the condition of sanitation facilities and presence or absence of a methane gas pit. Village-specific data pertaining to schistosomiasis endemicity, such as density of live intermediate host snails, density of infected snails and the mean *S. japonicum* prevalence among livestock, were obtained from village registries and the local schistosomiasis control station. Snail surveys were carried out from April to May by a trained group of field workers using a 0.1 m² square frame that was applied every 10 m. All snails within the frame were collected, grouped and counted at genus or species level. *O. hupensis* snails were crushed and examined microscopically to detect schistosome infections.

The location (latitude/longitude) of each village was determined by tracing the centre point of the village using a portable

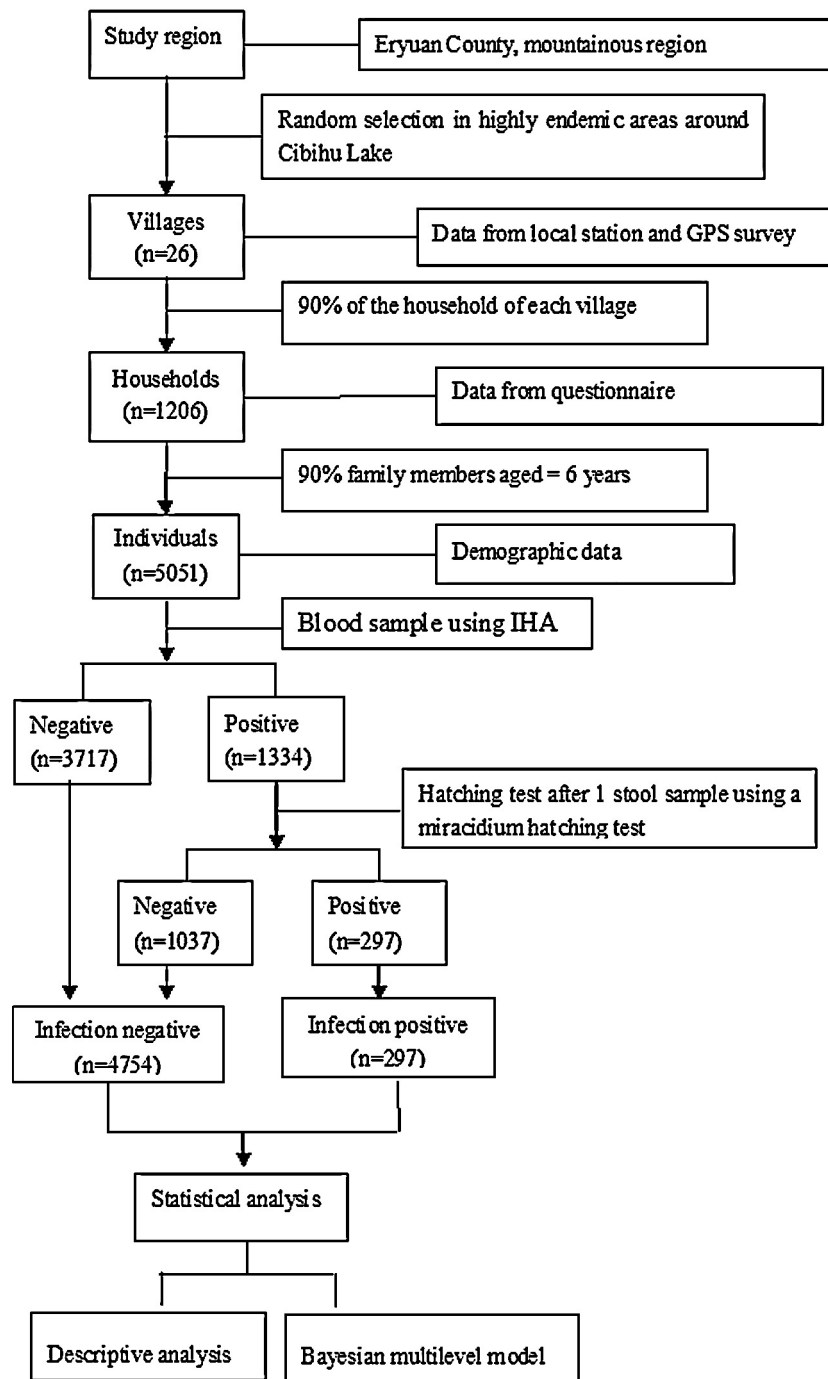


Fig. 2. Guiding framework of the current study in Eryuan county, Yunnan province, PR China in 2007.

global positioning system (GPS) unit (Trimble GeoExplorer; Trimble Navigation Limited, Sunnyvale, USA). Fig. 2 summarises the study procedures.

2.4. Descriptive statistical analysis

Data were double-entered and validated using EpiData version 3.0 (EpiData Association; Odense, Denmark). Analyses were performed using the statistical software package SPSS, version 11 (SPSS Inc.; <http://www.spss.com/>). Some continuous variables, such as age, size of farmland and number of livestock, were categorised based on the distribution of each variable, with a reference

category and a set of contrasted dummy variables, to explore the odds ratios (ORs) of each variable in the multilevel model.

2.5. Bayesian multilevel model

A Bayesian multi-level modelling approach that explicitly included spatial disease patterns and local environmental conditions was employed.

Considering the hierarchical nature of the data, a Bayesian multilevel analysis framework was developed with “individual data” assigned to level 1, “household data” to level 2 and “village data” to level 3 (Basáñez et al., 2004; Greenland, 2007; Yu et al., 2008).

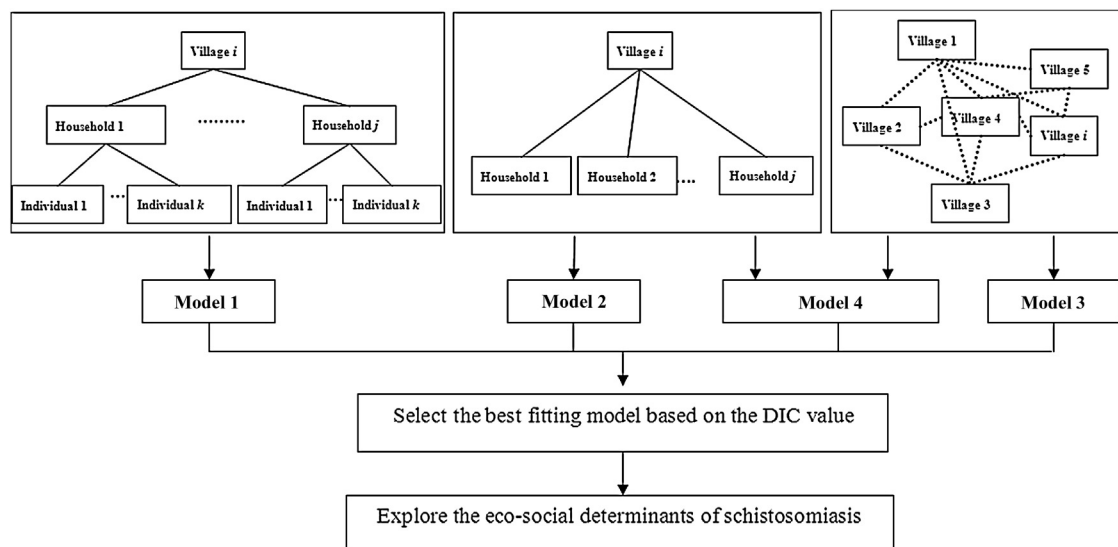


Fig. 3. The structure of the Bayesian models used in the current study.

The infection status (i.e. negative (0) or positive (1)) Y_{ijk} of individual k within household j at village i was assumed to follow a Bernoulli distribution ($Y_{ijk} \sim \text{Be}(p_{ijk})$), where p_{ijk} is the probability of being stool-positive. Serial multilevel logistic regression models were fitted with random effects ($u_j, j = 1, 2, 3, \dots, J$) at the household level, J being a member of the study households, random effects ($v_i, i = 1, 2, 3, \dots, N$) and spatial effects ($\varphi_i, i = 1, 2, 3, \dots, N$) at the village level, with N the number of study villages (Fig. 3).

The general Bayesian model, including all variables and random effects, was the following

$$\log \text{it}(p_{ijk}) = \alpha + \sum_n \beta_n X_n + u_j + v_i + \varphi_i$$

where the covariates X_n were the study factors at the individual, household and village level, u_j and v_i were the household- and village-specific random effects, respectively, and φ_i was the spatial effects between villages. These random effects were assumed to have a normal distribution; namely, $u_j \sim N(0, \sigma_1^2)$, $j = 1, \dots, J$ and $v_i \sim N(0, \sigma_2^2)$, $i = 1, \dots, N$, where σ_1^2 is the between-household variance and σ_2^2 is the between-village variance. The spatial correlation of φ was assumed to have a multivariate normal distribution, $\varphi \sim \text{MVN}(0, \Sigma)$, with variance-covariance matrix Σ . The spatial process was assumed to be an isotropic stationary process and Σ was defined as an exponential correlation function, $\sum_{ij} \sigma_3^2 \exp(-\rho d_{xy})$, where d_{xy} was the Euclidean (shortest straight-line) distance between village x and y , σ_3^2 was the spatial variance, and ρ was a smoothing parameter that controls the rate of correlation decay with increasing distance and measures the range of geographical dependency. The semivariogram analysis showed that the exponential model was superior compared to the spherical and Gaussian models. Thus, the exponential model was selected for subsequent analysis. For the exponential correlation function, the minimum distance at which correlation becomes <5% was defined by $3/\rho$ (Raso et al., 2006).

Model 1 only included the study factors at three levels without random and spatial effects; namely, $\log \text{it}(p_{ijk}) = \alpha + \sum_n \beta_n X_n$.

It was used to explore significant factors for further model building. Model 2 only included the study factors at household and village levels without random and spatial effects. Model 3 only included random and spatial effects without the study factors; namely, $\log \text{it}(p_{ijk}) = \alpha + u_j + v_i + \varphi_i$. Model 4 included the study

factors at household and village levels with random and spatial effects; namely, $\log \text{it}(p_{ijk}) = \alpha + \sum_n \beta_n X_n + u_j + v_i + \varphi_i$.

All models were fitted in WinBUGS 1.1.4 (MRC Biostatistics Unit; Cambridge, UK). Priors for the parameters were set based on the disease distribution and expert opinion. The prior distributions of both the sensitivity and specificity of each diagnostic test were based on expert knowledge and reference (Wang et al., 2006, 2008). The model parameters were estimated by employing the Markov chain Monte Carlo (MCMC) simulation (Gelfand and Smith, 1990). A single chain sampler with a burn-in of 30,000 iterations was run based on a trace plot for different prior starting distributions. The inference of the parameters was based on more than 15,000 iterations after the burn-in phase until the Monte Carlo error for each parameter of interest was less than about 5% of the sample standard deviation. The deviance information criterion (DIC) was used to compare the goodness of fit for the models. A model with a smaller DIC is considered to be a better fit (Spiegelhalter et al., 2002). All regression coefficients and associated 95% Bayesian credible intervals (BCI) of the posterior predictive median were computed via the Gibbs sampler. The exponential of these coefficients was used to obtain estimates of ORs and their corresponding 95% BCI. The WinBUGS modelling code is provided in Appendix A.

3. Results

3.1. Study cohort

Overall, 5051 individuals from 1206 families in the 26 selected villages of Eryuan County were eligible for inclusion. There were slightly more males ($n = 2567, 50.8\%$) than females ($n = 2484, 49.2\%$). Blood samples were collected from all individuals, and stool samples were submitted by 1334 participants with a positive IHA test. The overall positivity rate of the IHA test and miracidial hatching test for *S. japonicum* was 26.4% and 22.3%, respectively. The average schistosomiasis prevalence was 5.9%. At the unit of the village, the minimum and maximum prevalence was 1.2% and 9.0%, respectively. Data from 297 *S. japonicum*-infected individuals and 4754 uninfected controls could be considered for modelling. Questionnaire data were collected from all participating households. Table 1 shows the characteristics of the study cohort.

Table 1
Characteristics of the study cohort and estimates of parameters (posterior median with 95% Bayesian credible interval in brackets) in the multilevel models for infection with *S. japonicum* in 26 study villages in Eryuan county, Yunnan province, south-western PR China.

Level	Factor	Classification	Number (percent %)	Model 1 ^a	Model 2 ^a	Model 3 ^a	Model 4 ^a
Individual level	Intercept			−9.2 (−10.2, −3.7)	−9.0 (−11.9, −2.5)	−10.2 (−12.3, −3.7)	−8.4 (−12.6, 0.5)
	Gender ^b	Male	2567 (50.8)	1.0			
		Female	2484 (49.2)	0.9 (0.7, 1.3)			
	Years ^b	<10	525 (10.4)	1.0			
		11–20	1086 (21.5)	0.7 (0.5, 1.7)			
		21–30	914 (18.1)	0.7 (0.6, 1.8)			
		31–40	1192 (23.6)	0.9 (0.7, 1.9)			
		40–50	712 (14.1)	1.2 (0.3, 3.1)			
		>51	622 (12.3)	0.9 (0.7, 1.8)			
	House-hold level	≤2000 m ²	493 (40.9)	1.0	1.0		1.0
		>2000 m ²	713 (59.1)	2.8 (0.7, 54.1)	2.8 (0.9, 37.2)		4.3 (0.8, 12.6)
		≤2000 m ²	801 (66.4)	1.0	1.0		1.0
		>2000 m ²	405 (33.6)	1.6 (0.6, 2.5)	1.7 (0.8, 2.4)		1.3 (0.6, 1.4)
		Agriculture	479 (39.7)	1.0	1.0		1.0
		Agriculture and working outside	60 (5)	1.5 (0.4, 4.8)	1.4 (0.3, 3.9)		2.2 (0.7, 3.8)
		Agriculture and livestock	547 (45.4)	0.8 (0.4, 1.8)	0.8 (0.5, 1.9)		0.6 (0.4, 1.4)
		Agriculture and working outside and livestock	120 (10)	0.7 (0.2, 1.7)	0.8 (0.5, 1.5)		1.1 (0.9, 1.5)
		Tap water	27 (2.2)	1.0	1.0		1.0
		Others	1179 (97.8)	4.9 (0.1, 105.3)	5.1 (0.5, 85.9)		7.1 (0.8, 58.6)
		No livestock	194 (16.1)	1.0	1.0		1.0
		≤2	780 (64.7)	1.7 (0.5, 3.9)	1.8 (0.6, 3.9)		1.2 (0.8, 2.4)
		>2	232 (19.2)	2.9 (0.6, 9.7)	2.9 (0.7, 8.6)		4.1 (0.9, 6.9)
		Sanitary breeding stall	263 (21.8)	1.0	1.0		1.0
		No sanitary breeding stall	749 (62.1)	2.7 (1.6, 5.2) [*]	2.8 (1.7, 5.1) [*]		3.9 (2.5, 4.9) [*]
		No livestock	194 (16.1)				
		Breeding stall	194 (16.1)	1.0	1.0		1.0
		Breeding stall and dispersed feeding	302 (25.0)	0.7 (0.4, 1.7)	0.8 (0.5, 1.6)		0.8 (0.7, 1.5)
		Dispersed feeding	594 (49.3)	1.3 (0.5, 4.9)	1.3 (0.6, 5.2)		1.5 (0.7, 3.4)
		No livestock	194 (16.1)				
		Fixed	116 (9.6)	1.0	1.0		1.0
		No fixed	194 (16.1)	1.7 (0.4, 5.7)	1.7 (0.6, 5.8)		1.9 (0.4, 3.2)
		No livestock	194 (16.1)				
		Sanitary lavatory	148 (12.3)	1.0	1.0		1.0
		No sanitary lavatory	1058 (87.7)	1.3 (0.7, 2.5)	1.4 (0.5, 2.4)		1.6 (0.7, 1.8)
		No	215 (17.8)	1.0	1.0		1.0
		Having	991 (82.2)	1.2 (0.7, 1.7)	1.2 (0.8, 1.7)		1.3 (0.5, 1.9)
Village level	Infection rate of livestock of village		1.8 (−8.8, 13.5)	1.6 (−8.2, 12.8)		1.8 (−4.4, 8.5)	
	Snail density of village		1.4 (1.1, 11.9) [*]	1.4 (1.0, 11.2) [*]		2.8 (2.1, 8.4) [*]	
	Infected snail density of village		3.7 (2.3, 4.9) [*]	3.3 (2.8, 4.4) [*]		5.4 (2.1, 6.2) [*]	
Variation	Household-specific variation σ_1				0.2 (0.0, 0.4)	0.1 (0.0, 0.3)	
	Village-specific variation σ_2				0.9 (0.1, 1.1)	0.7 (0.1, 0.9)	
	Spatial variation σ_3				0.4 (0.2, 1.6)	0.2 (0.1, 1.3)	
Smoothing parameter ρ^c				1.1 (0.1, 2.7)	1.0 (0.3, 2.1)		
DIC ^d		1464.7	1386.8	1521.3	1131.2		

^a Credible intervals (or posterior intervals).

^b OR (Odds ratios) value for dummy variables.

^c Smoothing parameter is a scalar parameter representing the rate of decline of correlation with distance between points.

^d The deviance information criterion, the smaller value of DIC indicates a better fitting model.

^{*} Significant variables.

3.2. Outcomes of Bayesian multilevel models

Table 1 summarises the goodness-of-fit of our models for *S. japonicum* infection. The DIC value for model 2, which includes all three levels and a spatial random effect, was smaller than the corresponding value obtained for the other models, indicating that model 2 fits the data better than the other models.

3.3. Spatial pattern at village level

From the spatial correlation structures of *S. japonicum* prevalence in model 2, it follows that the shortest distance at which the spatial correlation is <5% is 2.9 km, which is considered the range of geographical dependency. This distance is more than the average geographical distance between neighbouring villages (2.0 km), suggesting that the *S. japonicum* infection pattern may be affected by neighbour villages. It also indicates that the spatial effects should be considered in model development and validation before wider use.

3.4. Eco-social determinants at different levels

According to the results listed in Table 1, the difference between age and years of *S. japonicum* egg-positivity show no statistical significance at the individual level (95% BCI of OR value including 1). At the household level, the key risk factor was the absence of a sanitary stall house for livestock breeding (OR = 3.9). At the village level, the primary risk factor was the density of living and infected intermediate host snails sampled in the village, with correlation coefficient 2.8 (95% BCI: 2.1–8.4) and 5.4 (95% BCI: 2.1, 6.2), respectively.

4. Discussion

The eco-social determinants of the transmission patterns of infectious diseases have been successfully considered in several epidemiological studies, and are supported by modelling approaches (Barreto et al., 2011; Cohen et al., 2007; Mossong et al., 2008). It is important to note that modelling is also increasingly utilised in various public health applications (Beaglehole and Bonita, 2000; Eisenberg et al., 2007; Patyk et al., 2013; Preston et al., 2013). Indeed, this approach can aid in improving the understanding of how and to what extent ecological and social processes affect the transmission of schistosomiasis and, more specifically, to unravel the fundamental role that social-ecological systems play in governing the frequency and disease transmission dynamics (de Souza Gomes et al., 2012; Utzinger et al., 2011; Yang et al., 2013; Zhang et al., 2012). In recent years, Bayesian statistics has permeated all major areas of the medical sciences, including epidemiology and public health, clinical trials, systematic reviews, meta-analysis, evidence synthesis, spatio-temporal modelling, survival analysis, time-series analysis, molecular genetics and decision-making (Ashby, 2006; Berry et al., 2010; Chammartin et al., 2013; Karagiannis-Voules et al., 2013). Bayesian statistics lend itself to identify risk factors and for assessing the impact of alternative environmental and social policies both at community and national levels as they can incorporate prior information about these into the analysis. The inclusion of prior information to improve estimates is a key feature that explains why a Bayesian framework is often more appropriate than classical mixed models (Basáñez et al., 2004; Bolstad, 2004; Possas, 2001).

Despite many years of integrated control resulting in predominantly low levels of prevalence and intensity of *S. japonicum* in the human population, there is concern that schistosomiasis might re-emerge in PR China, and hence sustained control efforts are still necessary (Steinmann et al., 2007a; Yang et al., 2008, 2009). Inherent challenges to achieve transmission interruption are the many

sources of infection (i.e. not only infected residents, but also many different species of infected livestock and wild animals serve as reservoir hosts of the disease) (McManus et al., 2010). Moreover, these residual sources of infection are difficult to remove. Hence, resurgence of schistosomiasis japonica is likely to occur should large-scale administration of chemotherapy be interrupted for several years (Chen, 2005; Guo et al., 2006; Wu and Huang, 2013; Zhou et al., 2007b).

According to the DIC value, we selected the Bayesian spatial multilevel model to investigate eco-social determinants. This model may thus be useful to identify issues to be addressed in subsequent policy and decision-making at the local scale. We established that the key risk factors for *S. japonicum* infection varied at different levels of the community (e.g. individual, household and village). For instance, absence of a sanitary livestock breeding stall at the household level and the distribution of living and infected snails at village level were the main contributors to the transmission of *S. japonicum*. This finding is fully supported by the life cycle of *S. japonicum*. Importantly, the local people can build breeding stalls for their livestock to avoid excreta of livestock contaminate the snail habitats, which in turn reduces the density of live and infected intermediate host snails to break the life cycle of *S. japonicum*.

A locally adapted, feasible and sustainable control strategy must consider the social-ecological context (Wang et al., 2009). Hence, a strategy to interrupt the transmission of schistosomiasis in hilly and mountainous regions of PR China must be based on the integration of all key factors at each level. At the individual level, information, education and communication (IEC) is an essential measure to decrease human exposure to water potentially containing cercariae (Guo et al., 2005; Zhou et al., 2013). At the household level, livestock management is a crucial aspect of control programmes in the hilly and mountainous region. This may differ from what has been applied in marshland and lake regions, namely the mechanisation of agriculture, thereby replacing livestock with tractors (Chen et al., 2004; Wang et al., 2009; Zhang et al., 2005). At the village level, environmental modification such as constructing fish ponds, digging new ditches and killing snails using molluscicides may be the most appropriate approaches to prevent infections among both humans and livestock. In general, a variety of biological and social factors govern schistosomiasis japonica in PR China. Social factors include those at national and regional level, such as policies and patterns of development, which impact on local economic activities and affect community-, household- and personal risk factors of infection. Huang and Manderson (2005) reviewed how social-structural and related factors influence individual risk and the community prevalence of *S. japonicum* in PR China, and showed that human infection was significantly related to work in rice fields infested with the intermediate host snail, and that the risk of *S. japonicum* infection was also influenced by the domestic environment, including both the location of the house in relation to snail-colonized water sources, access to safe water and improved sanitation.

Limitations of the current study must also be recognised. First, no behavioural information at the individual level, such as water contact duration, exact part of the body exposed to potentially infected water, etc., was collected. Second, the spatial distribution of schistosomiasis japonica cases is governed by exposure to infection over a period of time. Temporal correlation should thus be taken into account to improve model predictions.

We conclude that a Bayesian multilevel modelling approach can deepen the understanding of eco-social determinants at the local scale and that such a modelling framework can assist in designing evidence-based control strategies to interrupt the transmission of schistosomiasis in mountainous areas of the PR China. We believe that our approach will also contribute to a better understanding of

the epidemiology, control and eventual elimination of schistosomiasis elsewhere in PR China and beyond.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.actatropica.2014.04.013>.

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