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Schistosomiasis japonica: Modelling as a tool to explore transmission patterns

Jun-Fang Xu [a,b], Shan Lv [a,c], Qing-Yun Wang [d], Men-Bao Qian [a,c], Qin Liu [a,c], Robert Bergquist [e], Xiao-Nong Zhou [a,c,*]

[a] National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, Shanghai 200025, People's Republic of China
[b] Medicine School, Hubei University for Nationalities, People's Republic of China
[c] WHO Collaborating Center for Malaria, Schistosomiasis and Filariasis, Key Laboratory of Parasite and Vector Biology, Ministry of Health, Shanghai 200025, People's Republic of China
[d] Normal University of Gannan, Ganzhou, Jiangxi, People's Republic of China
[e] Ingerod, Brastad, Sweden

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ABSTRACT

Modelling is an important tool for the exploration of *Schistosoma japonicum* transmission patterns. It provides a general theoretical framework for decision-makers and lends itself specifically to assessing the progress of the national control programme by following the outcome of surveys. The challenge of keeping up with the many changes of social, ecological and environmental factors involved in control activities is greatly facilitated by modelling that can also indicate which activities are critical and which are less important. This review examines the application of modelling tools in the epidemiological study of schistosomiasis japonica during the last 20 years and explores the application of enhanced models for surveillance and response. Updated and timely information for decision-makers in the national elimination programme is provided but, in spite of the new modelling techniques introduced, many questions remain. Issues on application of modelling are discussed with the view to improve the current situation with respect to schistosomiasis japonica.

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1. Introduction

Schistosomiasis, one of the neglected tropical diseases (NTDs) and referred to as a "three factor disease" (schistosomes, snails and humans) by Kloos (1985), ranks high in priority in the light of socioeconomics and public health significance in tropical and sub-tropical areas. Several million people all over the world suffer from severe morbidity due to this disease (King, 2009; Taylor, 2008). Out of the six schistosome species adapted to humans three play a major role, i.e. *Schistosoma mansoni* in Africa, Middle East and Latin America, *S. haematobium* in Africa and the Middle East and *S. japonicum* in Southeast Asia (Chan and Isham, 1998). *S. japonicum* causes the most severe pathology (Chen and Mott, 1998) and the epidemiology is more complex than that of the other species

because of its zoonotic nature that involves more than 40 species of animal reservoirs, including cattle, dogs, pigs and rodents as discussed by Gryseels et al. (2006). The impact of schistosomiasis is not only related to Kloos' three factors, but also to demographic, environmental, political, socioeconomic and cultural factors (Collins et al., 2012). Modelling has made significant contributions to the surveillance and control of schistosomiasis. In spite of being used for *S. mansoni* and *S. haematobium* already before the 1990s (Bailey, 1986; Hammad et al., 1996), it has not been commonly applied for the study of *S. japonicum* transmission until recently. Thanks to the remarkably rapid development of the modelling methodologies during last decade, this approach now promises to take a leading role in the surveillance and control of *S. japonicum* transmission.

Epidemiological modelling could serve four major goals, such as: (i) a means of analysing risk factors in transmission; (ii) an aid to the interpretation of how transmission operates; (iii) a predictive tool for future transmission patterns; and (iv) a theoretical basis of formulating prevention and control policies for the national control programme. Two techniques have been applied, firstly mathematic modelling that covers application of differential equations (Chitnis

et al., 2012; Ishikawa and Ohmae, 2009; Michael et al., 2004; Ngwa and Shu, 2000; Schinaia, 2000; Swaminathan et al., 2008) and, secondly, statistical modelling including traditional statistics, Bayesian modelling and spatial statistics including spatio-temporal applications (Brooker and Clements, 2009; Cancre et al., 2000; Clements et al., 2006; Corner et al., 2013; Kloos et al., 1997; Sai et al., 2004a; Zhu et al., 2011).

The saying that "essentially, all models are wrong, but some are useful" (Box and Draper, 1987) demonstrates the dual characters of modelling. The approach can be wrong because of uncertainty and untested assumptions, but models can also be useful due to their focus on ill-defined areas (Dobson, 1999). In spite of this, modelling makes an outstanding contribution to the prevention and control of diseases in various ways. For example, some models have been used for building aetiological vistas by observing the association of risk factors with the occurrence of disease (Scott Hurd and Kaneene, 1993), while others have been used to assess the cost-effectiveness of disease control and practical instruction (Woolhouse, 1992). J. M. Keynes is supposed to have said that it is preferable to be roughly right than completely wrong. We have chosen to follow his advice by trying to explore the possibility of improving modelling in the area of surveillance and control of schistosomiasis japonica through scoping analysis using both statistical and mathematical models. This communication has been produced as a guide how to improve the information flow from field researchers to decision-makers with respect to elimination of schistosomiasis (Zhou et al., 2013). It is based on straightforward literature searches and the main body of the paper consists of presentation and discussion of the results of this research.

2. Approach

The literature search included documents on schistosomiasis japonica modelling, published from January 1, 1990 to December 31, 2011. The English literature was from ScienceDirect Onsite, SpringerLink Database and the PubMed Database. The Chinese literature came from Chinese National Knowledge Infrastructure (CNKI) database, the Wanfang Database and the VIP Database. Science Direct Onsite, Springer Link Database and PubMed Database are international databases based on English texts, while the other three databases are domestic and therefore exclusively produced in Chinese. We used the search terms: "schistosomiasis" or "schistosoma", "statistics" or "statistic model", and "model" or "modelling". Documents dealing with modelling schistosomiasis japonica by mathematic, statistic, and spatial techniques and methods, were included in the search.

2.1. Modelling in general

The purpose of modelling of the impact of schistosomiasis, regardless if the approach is statistical or mathematical can be summarised as: (i) description of interaction of factors that could possibly influence transmission; (ii) bringing all factors underpinning prevalence to light; (iii) prediction of prevalence trends; and (iv) disclosure of the theoretical foundations for control. As shown in Fig. 1, there are important and decisive relationships between the two kinds of the model. The major difference lies in the field of application. These statistical models are quantitative, biomedical tools, commonly used to summarise data related to epidemiological studies (Guyatt, 1998). Mathematical dynamic models applied for communicable diseases, on the other hand, emphasise the factors responsible for the mechanisms of transmission, dynamics of the infectious processes, for example providing threshold conception, such as the basic reproductive number (R_0), estimation of key parameters reflecting the various factors associated with transmission, elaborating transmission mechanism, and optimising control strategies (Chiyaka et al., 2010; Hu et al., 2010; Remais, 2010).

2.1.1. Statistical modelling

According to the two main streams of statistical concepts, the methodology applied generally involves traditional models based on the "Fisherian" philosophy (Efron, 1998; Gelman and Shalizi, 2013). This type of modelling consists mainly of "frequency approach" and "likelihood" methods. The former is one of a number of possible techniques of formulating generally applicable scheme for making statistical inference, i.e. frequentist inference. This is the basic framework of inference, such as the well-developed methodologies of unbiased estimators, hypothesis tests and confidence intervals. Likelihood is a function of the parameters of a statistical model and plays an important role in traditional statistic inference, especially methods of parameter estimation (Davison, 2008). Bayesian statistical models are the main alternative method based on the "Bayesian philosophy", which involves important concepts such as "prior and posterior knowledge", "prior, posterior and predictive distributions", and "Bayesian decision rules and estimators" (Hsu, 2005). The Bayesian approach to statistical modelling is characterised by perceiving all parameters/variables as random variables characterized by distributions. In a Bayesian analysis, all unknown parameters/variables are assigned prior distributions (Gelman and Shalizi, 2013). Posterior distributions constitute the solution to the analysis and can be summarised using point or interval summaries interpreted via probability-based reasoning. Bayesian philosophy offers a coherent method to statistical modelling, including building and fitting models with complex features, interpreting results, making inferences, and representing uncertainty (Balding et al., 2006).

Statistical models and techniques help applied researchers in the field of medicine and public health to extract and infer scientific and important conclusions from numerical data. With statistical models being increasingly complex, Bayesian statistics plays a more important role in application in all kinds of studies due to its flexible approach in modelling. In addition, application of spatial, statistical models have become increasingly used during the last 20 years due to the increased application of geographical information systems (GIS) and remote sensing (RS) techniques in epidemiology (Cailly et al., 2011; Chamaille et al., 2010; Shimabukuro et al., 2010; Zhou et al., 2009a, 2009b). The main application fields can be summarised as follows.

Traditional statistics has made great progress because of its wide area of application and played therefore a leading role in the statistical field. The most important feature of statistical models is that variability is represented by probability distributions. Typically, they must conform to both random and systematic variation. The difference between traditional statistics and Bayesian statistics lies mainly in their different interpretations of what probability signifies (Table 1). The traditional statistics theory of probability is only capable of dealing with random variables, which create a frequency distribution from "experience", i.e. they constitute a hybrid between two distinct methods of hypothesis testing that emphasize the decision between two, mutually exclusive hypotheses (Gigerenzer et al., 1991), while the Bayesian approach directly analyses the probability of each hypothesis, helping modellers develop an appreciation for values of explicitly, including uncertainty (Ellison, 1996). However, poorly defined prior probability distribution, which still constitutes the greatest difficulty in the development of Bayesian statistics, can distort results significantly. Meanwhile, there are much uncertainty and unknown information relative to schistosomiasis transmission, so it is necessary that we use well-designed prior distributions, which include definition of subjective probability, prior distributions and prior density.
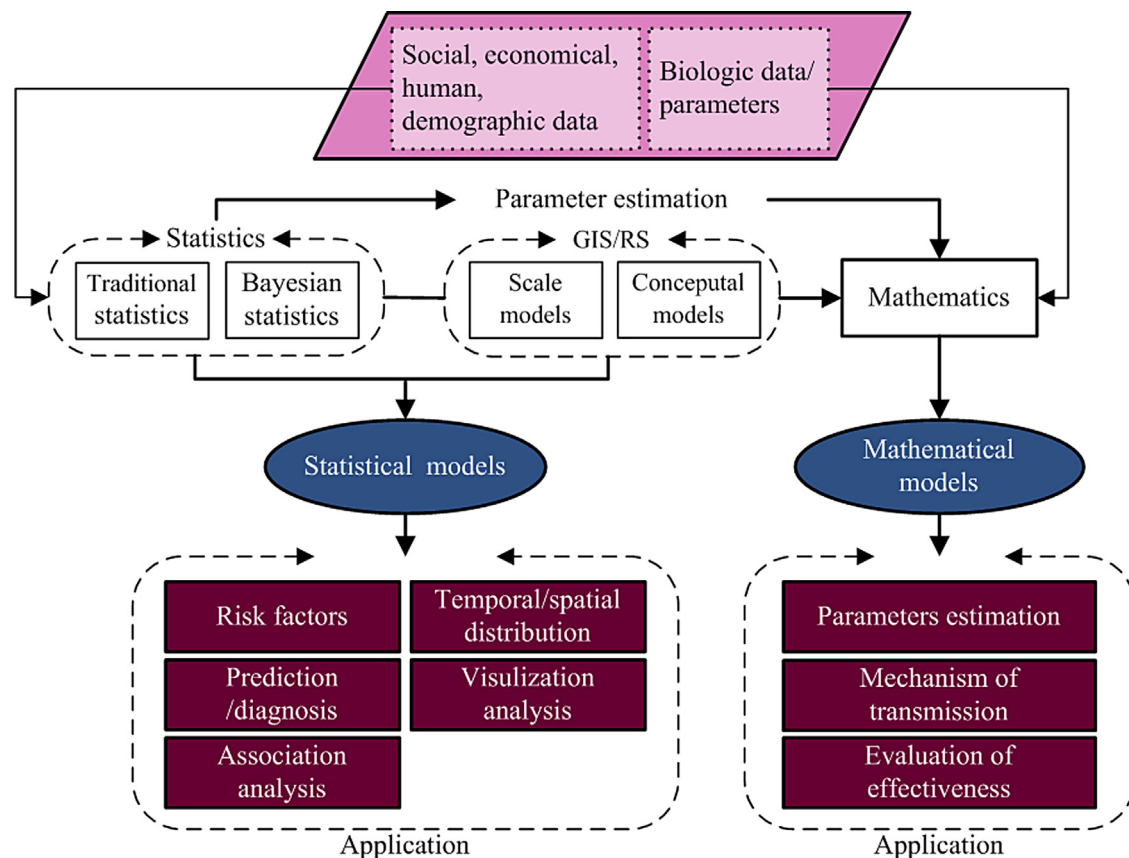
Fig. 1. The applications of modelling methods/techniques.

Spatial models discussed here are models combining GIS techniques with statistical methods, such as conceptual models (Gong et al., 2006; Liang et al., 2005). The GIS approach involves both specialised database management systems for handling spatial information and toolboxes of methods capable of manipulating spatial information. Conceptual models apply quasi-natural language or flowcharts to draw the components of the system under investigation and emphasize the linkages between them. This modelling approach is therefore an abstraction process that uses logical concepts, while hiding the details of implementation and data storage (Adnan Yazici and Akkaya, 2000). Conceptual models have been used to structure geographic phenomena and evaluate the relevance of existing rules for data and formats leading to a

conceptualisation of the real world, through which it is possible to develop tools to merge heterogeneous datasets. Applications of GIS in conceptual models can produce fuzzy, null output or incomplete information (such as lack of georeference information in some of locations) due to quantifiers of the spatial domain that might be difficult to manage as a result of certain degrees of uncertainty (Ferrè et al., 2014). So uncertainty should be considered for a powerful conceptual model that can be dealt with through explicit definition of the object identifier (Adnan Yazici and Akkaya, 2000). In addition, simplicity and orthogonality are important criteria for developing a powerful and intuitive conceptual model (Parent et al., 1999).

2.1.2. Mathematical modelling

Mathematical models are a great potential for the understanding of schistosomiasis transmission and the designing of control programmes. However, models must sufficiently reflect reality and groundwork in what is understood of the schistosome biology (Woolhouse, 1991). Medically-oriented mathematical models focus, for example, on studying on transmission mechanisms and can in this way evaluate the effects of control activities. It is widely acknowledged that the transmission processes of schistosomiasis japonica is considerably more complex in comparison to all the other schistosome species since its definitive hosts include more than 40 animal reservoirs. A great advantage is that also non-linear biological phenomena that often display very intricate patterns of dynamic behaviour, including chaos and multiple stable equilibriums, can be approached by means of mathematical modelling (Anderson, 1998). One of the main contributions of mathematical models to the field of communicable diseases is that they not only allow the study of diseases from a qualitative point of view but that they also open the possibility of dealing with quantitative concepts (Macdonald, 1965). However, mathematical models do

Table 1
Comparison of conventional statistics and Bayesian statistics.

	Traditional statistics	Bayesian statistics
Theory	Fisherian philosophy	Bayesian philosophy
Information sources	Sample information, general information	*A priori* information, general information, sample information
Definition of probability	Non-negativity, regularity, additivity	Subjectivity
Unknown parameter	Constant	Random variable
Selection rule of parameter estimator	Maximum likelihood	Minimum loss function
Hypothesis test	Statistic, sample distribution	Posterior probability
Judgement of hypothesis test	Significance level	Posterior probability
Evaluation rule	To include a series of rules	Fixed mode

not constitute a panacea, particularly because of the uncertainty of parametric estimations and the complexity of transmission models.

The primary use of mathematic models is to facilitate the formulation of intervention strategies by understanding the impact factors at play in schistosomiasis transmission as well as by their ability of simulating improved approaches. It is essential to better understand the impact that mathematical models can produce in local settings, particularly with respect to the identification of transmission mechanisms. Although this has been studied for almost a century, the characterisation of vulnerabilities of the parasite–snail–host interaction is still a challenge. Early on, the mathematical models mainly focussed on the population dynamics of schistosomes. For example, Hairston (1965), one of the first interested in the population biology of blood flukes, attempted to apply ecological life-tables for *S. japonicum* in the snail host and actuarial methods to study their population dynamics in human communities, later developed further by Anderson et al. (1985) and Hairston (1965). Later, models related to the transmission dynamics of schistosomes were developed (Macdonald, 1965). MacDonald's most significant contribution lies in formal treatment of the pairing success of dioecious trematode and the acknowledgement of its value in parasite transmission dynamics. His model encouraged others and led to various modified models (Gething et al., 2011; May, 1977; Nasell, 1976; Swaminathan et al., 2008). These changes of the original model resulted in the development of newer approaches that were closer to reality.

3. Fields of application

3.1. Statistical modelling

3.1.1. Analysing risk factors

The application of statistical models is useful for the understanding of risk factors that depend on schistosomiasis prevalence and the endorsement of reasonable allocation of resources (Bavia et al., 2001). Regression models are chiefly used to extract risk factors that can possibly influence schistosomiasis transmission, logistic regression in particular. The results reveal that risk factors relative to schistosomiasis infection/re-infection mainly include water-contact, individual immunity, past history of *S. japonicum* infection, which to some extent depend on the prevailing socio-economic situation, education level, age, occupation and residence (Gray et al., 2009; Ross et al., 1998a, 1998b, 1998c, 1997a; Seto et al., 2007; Tan et al., 2004; Yang et al., 2009; Zhang et al., 1997; Zhu et al., 2011). Factors relative to the disability weight of chronic schistosomiasis are chiefly clinical signs, such as abdominal pain, diarrhoea, hepatomegaly and hepatic fibrosis as well as impaired capacity for work or study, which varies with age, occupation and intensity of infection (Jia et al., 2007; Li et al., 1993; Xu et al., 2009; Zhou et al., 2005).

Studies of the impact of climate change on the distribution of vector-borne diseases naturally stress spatial risk factors and are related to the animal reservoirs and the ecological systems involved (De Casas and Carcavallo, 1995). Researchers have developed a series of spatial statistical models to explore risk factors relative to the climate and environment indicating the role of natural factors, including temperature, hydrology, altitude, vegetation coverage, soil types, soil moisture, water velocity, elevation, distance to snail locations and water, in particular with respect to snail distributions (Guo et al., 2005; Maszle et al., 1998; Peng et al., 2010; Raso et al., 2009; Sai et al., 2005; Seto et al., 2005; Wang et al., 2008; Yang et al., 2006; Zhang et al., 2009b, 2005). These spatial models are most often Bayesian and include geostatistical models, kriging, spatial scan statistics, network models of hydrological systems and spatial regression models.

3.1.2. Relationships between factors/variables

Another important application of statistical models is to evaluate the relationship between variables with various correlations to schistosomiasis transmission (Blume et al., 2007; Ross et al., 1997b; Wu et al., 2010; Zhou et al., 2004a, 2007). For example, Sun et al. (2003) established a nonlinear regression model to study the relationship between environmental temperature and the infection rate of *Oncomelania* snail, the sole intermediate host of *S. japonicum*. They estimated the lowest critical temperature for infection of snails with miracidia, and deduced that the infection rate descends with temperature. Theoretically, the *Oncomelania* snail cannot be infected with *S. japonicum* when the temperature is lower than 3.24 °C (Sun et al., 2003). Due to the lack of precise means for diagnosing schistosomiasis, Bayesian hierarchical models were developed to evaluate sensitivity and specificity of the examination method for *S. japonicum* in host populations (Carabin et al., 2005; Zhang et al., 2009a; Zhou et al., 2004b). Studies comparing the efficiency of serological tests (enzyme-linked immunosorbent assay, ELISA in short) and stool examination (Kato-Katz) suggest that it would be feasible to employ ELISA exclusively, rather than combining ELISA and stool examination for the estimation of the prevalence of *S. japonicum* infection in large-scale epidemiological settings (Wang et al., 2006). Other researchers combined data from GIS and RS with statistical models to explore the relationship between the rates of human infection and cattle infection in the endemic areas in the People's Republic of China (P.R. China) (Wu et al., 2007; Zhou et al., 2000). For example, applying spatial analysis, Wu et al. (2007) found that schistosomiasis is mainly concentrated in the marshlands along the Yangtze River. The results of their investigations based on linear correlation and regression analysis showed a positive correlation between infection prevalence in humans and in bovine, i.e. the slope of the linear regression decreased from 0.395 in 1989 to 0.215 in 2004 suggesting that the human prevalence and force of transmission in highly endemic areas have both been reduced, but the role of the bovine has instead become increasingly important. In parallel, other researchers used a nonparametric, spatial model to identify two significant high-risk regions for schistosomiasis by analysing surveillance data for acute schistosomiasis in P.R. China (Zhang et al., 2009c) finding that temporal or/and spatial aggregation with respect to the distribution of snails, parasite eggs and acute human cases.

3.1.3. Predicting schistosomiasis prevalence

Statistical models are valuable for predicting potential endemic areas of schistosomiasis and snail distributions. For example, it has been found that the level of January temperatures indicates the extent of potentially endemic areas (Zhou et al., 1998, 1999a, 1999b). This led to strengthening of research on the possible influence of global warming on schistosomiasis distribution in P.R. China. They also found that a temperature threshold (15.4 °C) for the development of *S. japonicum* within the intermediate host snail and a temperature (5.8 °C) at which half the snail sample investigated resorted to hibernation (Zhou et al., 2008). The spatio-temporal models have been used to predict the endemic situation in the areas of "construction of braking dikes or opening sluices for water storage" (Sai et al., 2006, 2004a, 2003, 2004b).

3.1.4. Estimating parameters

Statistical models can be used to estimate the parameters needed for the development of mathematical models of schistosomiasis transmission (Liang et al., 2005). Without well-estimated parameters, a mathematical model, e.g. for the estimation of schistosomiasis prevalence, is of little practical use. A Bayesian approach has been used to estimate key parameters for reducing model uncertainty (Liang et al., 2002). The transmission process for schistosomiasis is complicated, which also renders the mathematical

modelling complicated. In this complicated and somewhat messy situation, the Bayesian approach comes into its own, providing refined estimation and calibration of mathematical modelling estimates based on an iterative process that allows information from historic experience entering the calculation (Spear et al., 2002). The association between the intensity of infection in (reservoir) animals and humans can be estimated, suggesting that new measures of schistosomiasis control might need to be developed (McGarvey et al., 2006). Indeed, the association of non-human infections with human is an area of research that has already been considered (Wu et al., 2007; Yang et al., 2005, 2009; Zhou et al., 2011).

Regression models are common in the literature search on statistical models, which in our case included various approaches, e.g., single/multi-level logistic regression, generalized linear regression, stepwise regression, nonlinear regression, negative binomial regression, Poisson regression and auto-regression models. Out of these, logistic regression models are the most commonly used due to the interest in estimating the risk of an exposed group relative to that of a controlled or unexposed group (Hosmer and Lemeshow, 2000). Although the Bayesian method/technique is less often used than traditional statistical models in application for epidemiological studies of schistosomiasis, it is increasingly understood that it is better to analyse numerical data with random uncertainty than applying traditional statistical methods. The spatial models, applied together with GIS and RS results mainly provide the means for appraisal and monitoring of ecological transformation over large areas and through time, which may influence the identification, distribution, abundance and prediction of the intermediate host snail risk areas.

3.2. Mathematical modelling

3.2.1. Aid to interpretation of transmission mechanism

Many of models have been developed with the aim of understanding the various variables related to transmission dynamics and the parasite–snail–host interaction, including transmission velocity, transmission potentiality, basic reproductive rate, transmission threshold, and the equilibrium state of diseases transmission and their epidemiological significance (Wu and Wu, 2006). In addition to the parasite–snail–host interaction, the role of different hosts is also one of important issues in transmission, which could influence on the dynamics of this process. For example, the heterogeneity in human water-contact rates and acquired immunity of hosts, by weighting parasite per infected host, would impact on worm burden and/or parasite load (Barbour and Kafetzaki, 1993).

Mathematical models including human–cattle–snail have demonstrated that cattle plays a stronger role than the human for schistosomiasis transmission; this has been shown by analysis of the relation between the basic reproduction number R_0 and the death rate of snails, the recovery rate of human/cattle system, and it suggested that parasite treatment of infected cattle is more important for schistosomiasis control (Chen et al., 2010).

Mathematical models applied with data from GIS and RS can help us understand the dynamics of schistosomiasis transmission and identify spatial risk and population at risk. The climate and environmental factors are particularly involved in spatio-temporal transmission models. Factor of interest involve rainfall, water and air temperature, snail microenvironment temperature, daily precipitation, channel flows, etc. These variables can be pre-processed by statistical approaches and then used as input in mathematical models. By this kind approach, it has been shown that the transmission potential of schistosomiasis is very sensitive to climate changes on the periphery of the endemic areas and at higher altitudes within these areas (Martens et al., 1995). A new model, namely S. japonicum cellular automata (SjCA) model (Wan et al.,

2011), has been constructed to describe the changes of individual infection intensity. The SjCA model can simulate difference and interaction between individuals, which opens the possibility of analysing accuracy of individual simulations.

Muench (1959) referred to the way a catalyst operates in chemical reactions and presented an epidemiological model built on these principles. For example, the age-specific infection rate from serological data could be estimated by fitting a catalytic model reflecting the population features in the endemic areas, such as the prevalence, intensity of infection, infectivity, sex distribution, etc. (Wu et al., 1995; Xiu et al., 2006; Yu et al., 1998).

A stochastic model, based on the theory of negative binomial distribution, has been developed with the aim of facilitating the understanding of the features of variation in S. japonicum egg count. This has been used to produce a pocket chart to estimate the true prevalence (De Vlas et al., 1997; Yu et al., 2000).

3.2.2. Optimization of the control strategy

Many researchers have evaluated and compared the effectiveness of different strategies for schistosomiasis control in the endemic areas, particularly in low-level endemic areas. Models have often been used to guide the selection of strategies of schistosomiasis control by simulation (Wu, 2005; Zhuo et al., 1990). For example, mathematical models have shown that an integrated control strategy is effective and that other factors besides bovines might contribute to the local transmission (Zhou et al., 2011). Selective mass treatment, based on a dynamic model taking into account seasonal variations and measures for snail control (Ishikawa et al., 2006), has been shown to exert a conspicuous, sustained effect resulting in a clear decline of transmission of the disease. If only humans and bovines are treated, or short-term snail control is instituted as single approach, prevalence rebounds rapidly to endemic levels once chemotherapy or snail control is stopped (Ouyang et al., 2009; Williams et al., 2002; Zhao et al., 2011). Williams et al. (2002) have shown that an initial period of human treatment with praziquantel, a 45% improvement in human sanitation, and a 30% reduction of contact with contaminated water could achieve schistosomiasis elimination if applied jointly, but only the addition of a vaccination step would sustain this situation.

In addition to comparing different strategies, several studies have focussed on the study of finding the optimal intervention approach related to transmission parameters. For instance, age-targeted drug treatment strategies were explored by mathematical modelling with a system of partial, differential equations involving an age-dependent infection rate in human hosts and an infection age-dependent cercarial releasing rate in snails (Zhang et al., 2007). This study found that targeting the 11–20 years age group was the most effective. Drug resistance is a potential problem. Therefore mathematical modelling which includes the age of infection in the snail, the density-dependent reproduction rate of snails, the distribution of schistosomiasis in the human population and drug treatment of the human hosts, could theoretically establish an explicit threshold of the treatment rate (Feng et al., 2002). Mathematical models including the human–water buffalo–snail system demonstrated that even at low levels of prevalence and infection intensity, the water buffalo plays a more important role with regard to transmission than the human host, predicting that parasite reproductive rates would not sustain the level of risk without the contribution of the water buffalo (Gray et al., 2008).

Mathematic models, based on the knowledge of the inter-relationship among schistosomiasis, the hosts, climate and environmental factors, have allowed researchers to develop and compare various control strategies and provide guidance towards optimal approaches, which supports decision-making. A worm-burden model with ordinary differential equations (Liang et al., 2002), which incorporate the general biological parameters with

the local environmental ones, explored effective schistosomiasis control strategies in different environments. The result showed that treatment of the student group is a key to reduce the output of parasite eggs to the environments. Sustainable control strategies are essential in controlling schistosomiasis transmission. These strategies include chemotherapy, focal snail control and egg control (Liang et al., 2005). A spatio-temporal schistosomiasis transmission model could easily examine the effect of schistosomiasis control, and improve its effectiveness (Gong et al., 2006). The connectivity of host populations has been studied through combination mathematical models with GIS showing that it would be possible to influence the connectivity of host populations through the construction of better infrastructures, for example road and water resources development (Seto and Carlton, 2010). Recent research has indicated that the extensive use of praziquantel, together with the molluscicide (e.g. niclosamide), has lowered transmission to levels where it has become difficult to detect prevalence and intensity of disease by continued reliance on acute schistosomiasis case reports or regular surveys of *S. japonicum* infection in humans and/or snails (Spear, 2012; Spear et al., 2011). However, sensitive areas still need more surveillance and response activities.

Evaluation of the cost-effectiveness of control strategies contributes to management of schistosomiasis control programmes. Mathematic models were for this purpose and used to evaluate the rational allocation of available resource for screening and chemotherapy, which involved population infection rates, and the ratio of infection rate to cost for screening and chemotherapy, sensitivity and specificity of screening methods (Chen et al., 1996).

4. Gap analysis

4.1. Descriptive summary of the literature searched

We collected 73 articles on modelling tools applied in the epidemiological study of schistosomiasis japonica; 48 articles concerned statistical modelling and 25 articles mathematical modelling (Table 2). The period 1990–2000 was dominated by traditional statistics, while the period 2001–2010 had an increasing trend of spatial statistics beside more traditional papers. Spatial modelling had already started to increase in epidemiological studies of schistosomiasis in the mid-1990s and after the year 2000, Bayesian statistical models became more common (Liang et al., 2002). The application of statistical modelling focussed on analysing risk factors relative to schistosomiasis transmission. While mathematical modelling was chiefly applied to the study of transmission mechanisms in the 1990s, optimization of control strategies became the main focus in the period of 2000s.

4.2. Research foci

Statistical models are more focussed on the study of risk factors: (i) extracting risk factors (Yang et al., 2006); (ii) quantitative analysis of the relationship between variables (Wu et al., 2007); and (iii) prediction or causal inference (Steinmann et al., 2007). In most situations related to schistosomiasis field research, Bayesian statistics are superior. The reason is that it: (i) answers truth/false questions when research hypotheses are tested, such as evaluating sensibility and specificity of various diagnostic approaches (Wang et al., 2006); (ii) estimates unknown parameters more accurately, such as some of the variables used in mathematical models for reducing the uncertainty (Liang et al., 2005); and (iii) is flexible, not only easy to apply and analyse, but also to understand complicated phenomena, particularly data with spatial and temporal attributes (Yang et al., 2005). Mathematical models are particularly useful for the study of transmission dynamics: (i) simulating the dynamical process of

schistosomiasis transmission (Gray et al., 2008); (ii) calculating the transmission threshold of schistosomiasis (Zhuo et al., 1990); and (iii) evaluating, comparing, optimizing control strategies through transmission simulation (Hu et al., 2010; Li et al., 2012; Yang et al., 2005).

4.3. Important findings

The advantages of statistical modelling are twofold. First, the role of risk factors impacting on schistosomiasis transmission varies with the spatial scale, e.g. individual factors including individual behaviour, health habits, individual immunity are all important at for small-scale changes of the transmission process, while ecological factors including distance to the positive snail sites, vegetation of snail sites are large-scale variables (Chen et al., 2007; Remais, 2010; Zhou et al., 2008). Second, the development of the schistosome stage inside the snail is mainly affected by temperature, which has been used for the study of the impact of climate changes on the distribution of schistosomiasis japonica. For example, by using the research results that temperature threshold for the development of *S. japonicum* within the intermediate host snail is 15.4 °C, and the critical temperature of environment for infection of snails with miracidia is theoretically 3.24 °C, the potential risk areas under the climate change scenario could be projected (Zhou et al., 2008).

With respect to mathematical modelling, the main findings also revealed two aspects. First, the role of different definitive hosts of schistosomiasis japonica varies in different local settings. The water buffalo plays a more important role, accounting for more than 75%, of all transmission, which is much more than the role played by humans supporting the notion that the human–snail–human cycle is currently relatively minor, at least in the lake regions (Williams et al., 2002). Second, control strategies varies also with prevalence levels, environmental settings, target populations and so on (Chen et al., 2007; Hu et al., 2010; Li et al., 2012; Liang et al., 2002; Zhou et al., 2011).

5. Discussion

5.1. Challenges and opportunities

The contributions of modelling for the epidemiological studies of schistosomiasis are outstanding, such as it has been shown the calculation of hibernation and role of temperature for the development of snails and the parasite inside. This has made it possible to produce a reliable transmission index of schistosomiasis, extracting high-risk factors and predicting future prevalence of schistosomiasis. However, many problems remain. One reason is that the fight against schistosomiasis takes place in the face of ecological diversity, global warming, population movements, and local re-emergence of schistosomiasis japonica and so on. The current challenge is to establish strong health systems capable of caring properly for patients and to integrate sustainable control measures. Another reason is that modelling methods are in themselves not enough to solve all problems.

5.1.1. Statistical models
The fundamental idea of statistical models is to treat observed values as random variables from a random sample (Davison, 2008). Indeed, sampling variations may impact the precision of parameters estimation in models, so attention should be paid to the problems relative to sampling, such as sampling units, sample schemes, optimum allocation of sampling units to various strata, sampling with varying probabilities and so on. For example, most previous studies selected the scales of survey based on administrative regions rather than geographical areas. There is evidence that

Table 2
Descriptive summary of the literatures.

Modelling			1990–2000		2001–2010		Total	
			Number	%	Number	%	Number	%
Statistical modelling	Technique/methods	Traditional statistical modelling	6	54.6	12	32.4	18	37.5
		Bayesian modelling	0	0.0	8	21.6	8	16.7
		Spatial statistical modelling	4	36.4	12	32.4	16	33.3
		Time series modelling	1	9.1	4	10.8	5	10.4
		Others	0	0.0	1	2.7	1	2.1
	Application	Analysing risk factors	6	54.6	18	48.7	24	50.0
		Relationships between factors/variables	2	18.2	11	29.7	13	27.1
		Predicting the schistosomiasis prevalence	3	27.3	4	10.8	7	14.6
		Estimating parameters	0	0.0	4	10.8	4	8.3
Mathematical modelling	Technique/methods	Mathematical modelling	5	83.3	18	94.7	23	92.0
		Mathematical modelling, GIS	1	16.7	1	5.3	2	8.0
	Application	Aid to interpretation of transmission mechanism	4	66.7	4	21.1	8	32.0
		Optimization of the control strategy	2	33.3	15	79.0	17	68.0

a model can be extended within the same ecological zone, but not across different ecological zones which might be the same administrative region (Brooker et al., 2002), so better selection of study sites is important, if the model includes too many geographical factors (Yang et al., 2011). In addition, identifying residual errors is important for statistically modelling (Freedman, 2009). There is an annoying and often sizeable difference between the necessarily idealized theoretical basis for the models and their regular application in practice. The difference is made up of residual errors, which carry significant information concerning the appropriateness of assumptions, so analysis may involve informal graphics to show general features of the residuals as well as formal tests to discover specific departures from potential assumptions. However, we found that there were few reports including analysis residual errors in the most papers about application of statistical models for schistosomiasis. From the statistical viewpoint, there are unknown problems for residual errors in models, such as the origin of these errors, what residual errors means and why they require statistical features. Explanation of models may be limited by these problems.

5.1.2. Mathematical models

The reliability and rationality of mathematical models are most important for system design. It is therefore necessary that the modeller select an appropriately model structure to make conclusion effective and modelling simple. For example, it stands to reason that it would be useful to consider association between different populations (human and reservoir animal hosts) and time delay for schistosomiasis. Next, screening and identifying parameters are key for the certainty of models (Spear and Liang, 2011). In reality, some parameters are not easily available. Thus, it is helpful that data can be analysed by statistical methods and the phenomena how the results vary with numerical value of one/more parameters are observed through computation simulation. For example, Bayesian statistical methods are used to estimate key parameters in mathematical models, which can reduce uncertainty of models. Finally, deterministic models, such as difference equation, differential equation, integral equation, or functional differential equation, are primarily considered, because they are relatively simple to explain for health public workers, and this can solve some problems (Ma et al., 2004).

In recent years, a new model—the meta-population mathematical model, has been applied to the biology field. It involves explicit movements of the individuals between different areas, and movement cannot only correspond to an actual physical movement of individuals, but can also manifest the evolution of a feature (Ma et al., 2009). The meta-population model was applied to study the spread of malaria to non-endemic areas and the interactions between rural and urban areas are given (Arino et al., 2012).

Therefore, it is introduced in the context of epidemiological studies of schistosomiasis to take spatial heterogeneity into account.

Combining statistical methods, GIS and computer simulations with dynamic methods could make modelling more realistic, more reliable and also contribute to a better understanding of schistosomiasis transmission (Ma et al., 2009; Yang et al., 2012).

6. Research priorities and conclusions

Modelling is playing an increasingly important role in the fight against schistosomiasis (Zhou et al., 2009a). Changes of the societies, cultures and the environments have accelerated in recent years, leading to a higher complexity of transmission-related problems. This higher complexity comes with new challenges for modellers. Modelling promises further progress with respect to schistosomiasis epidemiology but to take advantage of this trend, we need to pay attention to detailed variations of the dependent parameters.

Author's contributions

JFX and XNZ conceived and wrote the first version of the manuscript. JFX, SL, MBQ, QL, RB and XNZ revised the manuscript. XNZ finalised the manuscript. All of authors read and approved the final version of the manuscript.

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