

Schistosoma japonicum risk in Jiangsu province, People's Republic of China: identification of a spatio-temporal risk pattern along the Yangtze River

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Abstract. The risk for *Schistosoma japonicum* infection in Jiangsu province, People's Republic of China, was investigated by a mouse bioassay. Various investigations were conducted in the period 2009-2011 with the presentation here representing the summary of the results from 45-50 sites in the marshlands along the Yangtze River's course through the province. Indices representing three aspects of the infection were collected to assess risk: (i) the proportion of sentinel points where at least one mouse infection was recorded; (ii) the proportion of infected mice at each of these sites; and (iii) the average worm burdens. Directional distribution analysis and scan statistics were used to explore the spatio-temporal risk pattern. The spatial distribution was oriented along the Yangtze River and the directional distributions for the proportion of infected mice and mean worm burdens were similar for the positive sentinel sites. Four statistically significant clusters were detected in 2009, but only one in 2010 and 2011, respectively. Temporal windows for infection risk were seen in June and September. The study illustrates the utility of spatio-temporal analysis in assessing the risk for schistosomiasis. This approach should be useful with respect to surveillance and response that can be expected to be increasingly applied when moving from morbidity control to transmission control.

Keywords: schistosomiasis, mice bioassays, spatio-temporal analysis, schistosomiasis transmission control, risk area, People's Republic of China.

Introduction

Schistosomiasis japonica is a zoonotic disease caused by infection with the trematode parasite *Schistosoma japonicum*, which depends on *Oncomelania hupensis* snails as its intermediate host. The snails release cercariae, which infect humans by penetrating the skin during water contact such as fishing, cultivating crops, cutting weeds, washing clothes, swimming, etc. The disease was once a major public health problem in the People's Republic of China (P.R. China) with up to 12 million cases, but the number of infected people has gradually been reduced to less than

500,000 (Utzinger et al., 2005). However, approximately 65 million individuals are still at risk (Zhou et al., 2005, 2007). Schistosomiasis remains endemic in many, limited foci in the hilly and mountainous regions in Sichuan and Yunnan provinces, but the main problem is in the marshlands and lakes in the eastern and central parts of the country, where elimination of transmission has proved difficult to achieve (Utzinger et al., 2005; Hao et al., 2006). Here, more than 80% of all current cases in the country are found in a wide belt covering the provinces of Hunan, Hubei, Jiangxi, Anhui and Jiangsu.

Jiangsu province is located in the lower reaches of the Yangtze River along the East Coast of P.R. China (Fig. 1). It plays an important role in the Chinese growth of business and the socioeconomic changes and environmental upheavals (landslides, flooding) during the last few decades first resulted in an increase in the distribution of schistosomiasis here. The increased extent of snail habitats and intensity of transmission produced a highly endemic situation with higher numbers of acute

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cases then before (Huang and Manderson, 2005; Sun et al., 2008). As late as in 2004, 35 counties in Jiangsu province were endemic with 39 acute cases reported (Huang et al., 2004; Yang et al., 2005). Responding to this, the provincial government revised control strategies in 2005, strengthening integrated measures such as applying expanded chemotherapy for humans and bovines together with snail elimination, improved water supply, sanitation, personal protection and health education (Sun et al., 2011). These extensive, integrated control activities were successful and all endemic counties in Jiangsu province had reached the criterion of transmission control by 2010 (i.e. infection levels below 1% both in humans and livestock and no infected snails found during routine surveys) transforming the province into a low-endemic area (Hong et al., 2011; Sun et al., 2011, 2012). However, low levels of infection persist, and this together with the relative insensitivity of the Kato-Katz stool examination technique makes it difficult to identify the extent of risk (Lin et al., 2008). Since a technique capable of reliably detecting low levels of transmission is critical for schistosomiasis control, we developed an integrated approach consisting of water contact studies based on sentinel mice and spatio-temporal analysis to assess the infection risk and explore the potential for moving towards complete elimination of schistosomiasis transmission (Collins et al., 2012). The presentation is the summary of a number of transmission projects carried out in various areas along the Yangtze River during 3 years.

Materials and methods

Study area and time periods

Studies took place from 2009 to 2011 between May and September of each year in the marshlands along the Yangtze River within Jiangsu province. The investigations covered 19 counties and the total length of river bed investigated was about 180 km. The sites chosen for monitoring (Fig. 1) were selected based on the following factors:

- (i) assembly centres of mobile boatmen and fishermen in snail-containing environments;
- (ii) assembly centres of large enterprises, construction projects and docks along the Yangtze River;
- (iii) administrative boundaries of villages;
- (iv) sites where infected snails have been found in the past 3 years; and
- (v) livestock grazing areas and waterways in direct connection with the Yangtze River.

Sentinel mice

A mouse bioassay was developed to standardise and improve the sensitivity of water contact studies for schistosomiasis risk. It consisted of wire cages, each with 20 mice weighing 20 g or more, that could be suspended at the water surface to ensure that tails, paws and portions of the lower abdomen touched the water. The cages were deployed at various sites along the river on a monthly basis exposing the mice to surface water for

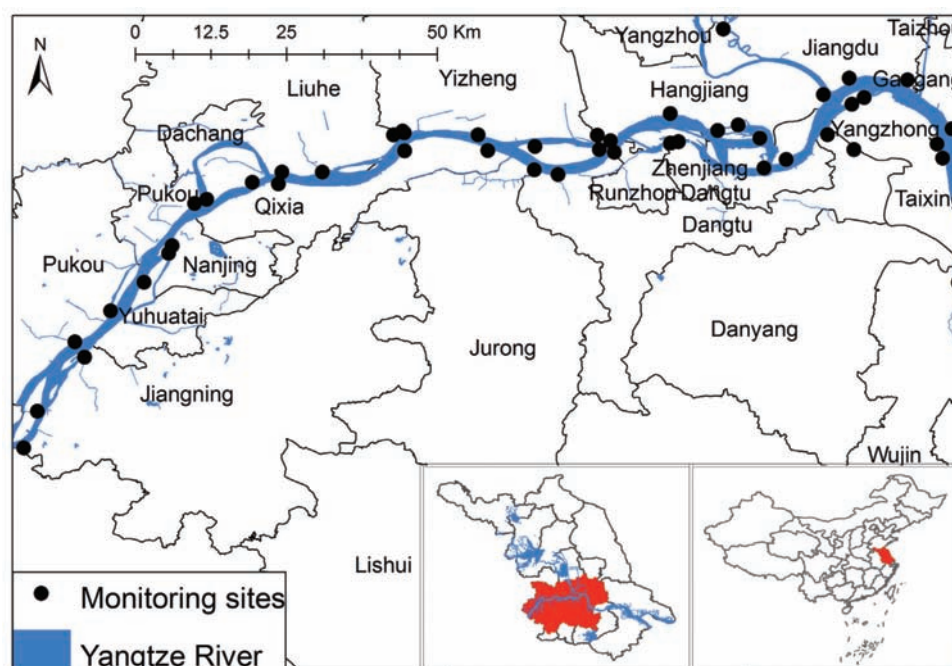


Fig. 1. The study region with the location of the surveillance sites in Jiangsu province, P.R. China.

two consecutive days between 10:00 and 14:00 hours, after which the mice were brought to the laboratory and raised for 5 weeks to allow the development and maturation of any parasite resulting from an infection in the water. The mice were subsequently sacrificed, perfused and their livers sectioned and subjected to microscopy. Mice with adult schistosome worms in their veins or with eggs in their livers were recorded as infected.

One project in 2009 was based on 45 sites along the river, whilst others in 2010 and 2011, respectively, utilised 50 sites. Geographical coordinates (latitude/longitude) at each site were recorded by a hand-hold geographical positioning service (GPS) device (Garmin Map76 (Garmin Corp; Taiwan)). The GPS data and the laboratory results emanating from the sentinel mice were integrated into a geographical information system (GIS) database to assess the infection risk. The following three indexes were used:

- (i) the proportion of sites with infected mice, i.e. the number of surveillance sites with positive mice compared to the total number of surveillance sites;
- (ii) the proportion of infected sentinel mice, i.e. the number of positive sentinel mice out of the effective number of sentinel mice, i.e. the total number of mice minus those that succumbed and died for various reason during the field work; and
- (iii) the average worm burden, i.e. the total number of worms recovered in relation to the total number of positive sentinel mice.

Ethical approval

All mice studies described here were approved by the Ethics Review Committee of Jiangsu Institute of Parasitic Diseases, P.R. China (permission no. JIPDERC2007008).

Statistical analysis

Primary descriptive analysis

The changes over time at the positive sites, rates and worm burdens were first explored through visual inspection including calculation of the mean values and dispersions, then compared using a χ^2 test. The analyses were performed using SPSS (version 11, SPSS Inc. Chicago, USA).

Spatio-temporal analysis

All spatially explicit analyses were carried out using the spatial analyst module of ArcGIS 10.0 (ESRI;

Redlands, USA), which has been widely applied in many fields of research (Oyana et al., 2006; Lai et al., 2009; Svensson et al., 2009; Naparus and Kuntner, 2012). The standard deviational ellipse (SDE) measures the spatial distribution of geographical features and provides information about dispersion in terms of orientation and deviation. The “directional distribution application” was used to measure whether the distribution at the positive sites, the positive rates and worm burdens exhibited an annual, directional trend and to provide information about dispersion in terms of compactness and orientation. Distributional trend analysis was used to create a feature class containing an elliptical polygon centred on the mean centre for all features under investigation. The attribute values for these output ellipse polygons were three-fold, i.e. the two standard distances (the long and the short axis) plus the orientation of the ellipse. One standard deviation (SDE1) was used to represent the ellipse polygon covering approximately 68% of all input feature centroids (Svensson et al., 2009; Naparus and Kuntner, 2012). A series of measurements and data including axial ratios, length of the long axis, length of the short axis and the feature coordinates for each ellipse were collected to compare the spatial risk patterns.

The SaTScan™ method has become an increasingly popular adjunct for exploring the spatio-temporal distribution of infectious diseases (Kulldorff, 2001; Kulldorff et al., 2005; Higgs et al., 2007), and more and more studies in P.R. China use it to confirm cluster results and to explore disease patterns (Zhang et al., 2008; Li et al., 2009; Zhao et al., 2010). Clusters of the positive rates of sentinel mice were identified by this methodology. SaTScan™ (version 9.1) was used to identify clusters of high and low risk by the space-time permutation model, defined by a cylindrical window constrained to clusters with both the proportion of the population at risk and study periods less than 50% (Coleman et al., 2009; Le et al., 2012). Relative risk (RR) for each cluster was also calculated. RR is the estimated risk within the cluster divided by the estimated risk outside the cluster. It is calculated as the observed divided by the expected within the cluster divided by the observed divided by the expected outside the cluster. The mathematical notation is:

$$RR = \frac{c / E[c]}{(C - c) / (C - E[c])}$$

where the number of c is observed cases within the cluster, C is the total number of cases in the data set and $E[c]$ is the expected number of cases within the cluster (Mainassara et al., 2010). Monte Carlo simulations (999 times) were used for significance testing at the 0.05 level.

Results

Tables 1 and 2 summarise the results of the bioassay by month and year. Altogether, 18 positive sites were recorded out of the total of 725 corresponding to a positive rate of 2.5%, while the number of infected mice discovered was only 53 out of all the mice deployed over the 3-year period (13,100) corresponding to a positive rate of 0.40%. A total of 167 adult schistosome worms were collected from these 53 positive mice giving an average worm burden of just above 3 worms per mouse (3.15). The monthly and yearly ranges over the 3 years were 2.00-5.70 and 2.30-4.00, respectively.

Figs. 2 and 3 show the developments over time for the study sites sentinel mice by month and year. The variances were significant ($P < 0.01$). Fig. 2 shows a minimum around July and indicates increased risk in the beginning and end of the season with two peaks of infection: one in June and one in September. The graph in Fig. 3 shows clearly the declining rates. Interestingly, however, even if the number of infectious sites declined strongly from 2009 to 2011, the risk at each infectious site actually climbed slightly in 2011.

Fig. 4 shows the series of directional distributions of the positive rates of sentinel sites, mice and worm burdens. The purple, green and red ellipses represent the directional distributions for 2009, 2010 and 2011, respectively. These directional distributions were simi-

lar and the ellipse orientations were always oriented along the Yangtze River. From 2009 to 2010, the lengths of both axes became increasingly reduced, indicating that the standard deviations of the ellipses were decreasing. Fig. 5 shows the overall, directional distribution of the positive rates of sentinel sites, mice and worm burdens. The orientation of the ellipses was similar, but both worm burden axes were shorter than those of the other two, indicating that the standard deviation of the worm burdens was lower.

Table 3 and Fig. 6 present the results of the scan statistics for the positive sentinel mice and the distribution of the cluster circles. Four statistically significant clusters were discovered in 2009 but in 2010 and 2011, there was only one each year. Dantu was the only county that presented a cluster for every year investigated. The clustering occurred in June and September with the relative risk being the highest in June.

Discussion

Spatio-temporal identification of regions at risk for schistosomiasis infection is the first step when replacing general control activities by a move towards elimination. In line with the remarkable progress in schistosomiasis control made in P.R. China over the last 60 years, Jiangsu province has become a low-endemic area. However, the extent of infection risk is assessed on conventional surveillance systems, focused on

Table 1. Summary of monthly findings from 2009 to 2011.

Month	No. of sites investigated	Positive sites	Positive rate at the site*	Total number of mice	Mice found positive	Positive rate in mice**	Worms per mouse	Average worm burden
May	145	2	1.4%	2,749	8	0.29%	28	3.50
June	145	4	2.8%	2,633	8	0.30%	16	2.00
July	145	2	1.4%	2,660	3	0.11%	17	5.67
August	145	2	1.4%	2,475	19	0.77%	61	3.21
September	145	8	5.5%	2,593	15	0.58%	45	3.00
Total	725	18	2.5%	13,110	53	0.40%	167	3.15

* $\chi^2 = 7.75$, $P = 0.101$; ** $\chi^2 = 17.22$, $P = 0.002$.

Table 2. Summary of annual findings.

Year	No. of sites investigated	Positive sites	Positive rate at the site*	Total number of mice	Mice found positive	Positive rate in mice**	Worms per mouse	Average worm burden
2009	225	13	5.8%	4,355	23	0.53%	53	2.30
2010	250	3	1.2%	4,252	12	0.28%	42	3.50
2011	250	2	0.8%	4,503	18	0.40%	72	4.00
Total	725	18	2.5%	13,110	53	0.40%	167	3.15

* $\chi^2 = 14.71$, $P = 0.001$; ** $\chi^2 = 3.24$, $P = 0.198$.

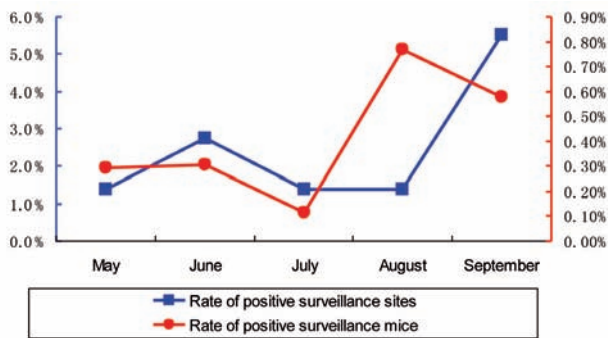


Fig. 2. The monthly positive rates.

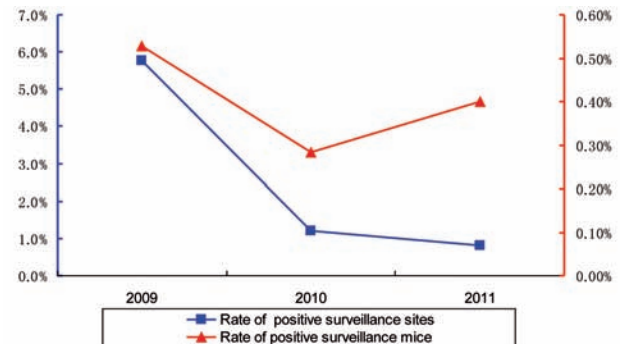


Fig. 3. The annual positive rates.

humans and the intermediate host, which are not sufficiently sensitive. The mouse bioassay for risk detection, expressed by the presence of cercariae in the water, has become increasingly used as an early warning system (EWS) for schistosomiasis (Spear et al., 2004; Worrell et al., 2011). We preferred this approach as it is a considerably more sensitive than conventional stool examination and lends itself to standardisation.

The impact of ecological factors on the transmission

pattern of schistosomiasis has been well documented in many epidemiological studies with the support of spatial modelling (Simoonga et al., 2008; Yang et al., 2009). Application of spatial technologies for schistosomiasis epidemiology, including GIS, remote sensing and geostatistical analysis, have provided important advances in our understanding of the key factors governing transmission of this disease (Yang et al., 2008, 2009; Zhou et al., 2009; Malone et al., 2010). Spatio-temporal analysis modelling allows the investigator to

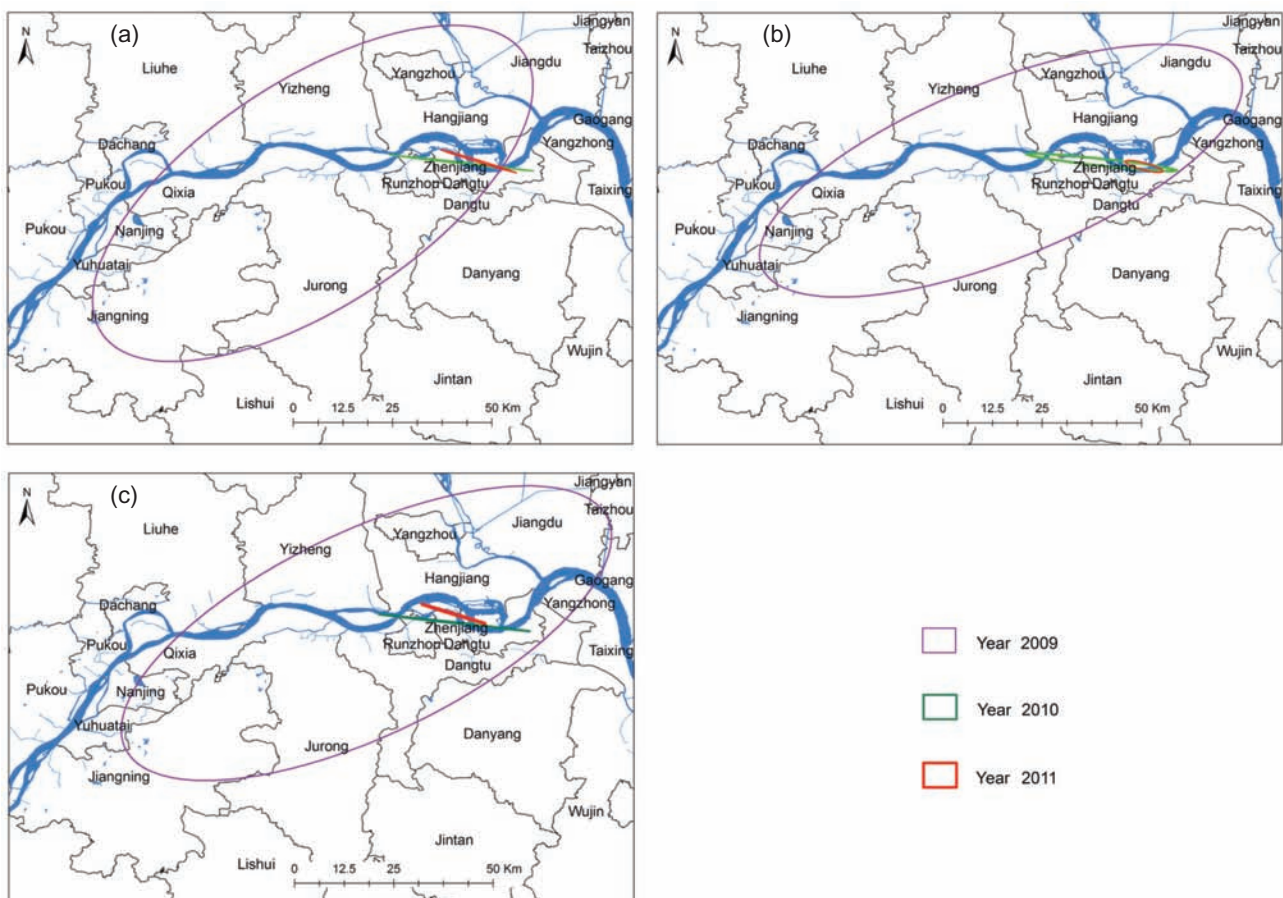


Fig. 4. The directional distribution of the positive rates of surveillance sites (A), sentinel mice (B) and their average worm burden (C).

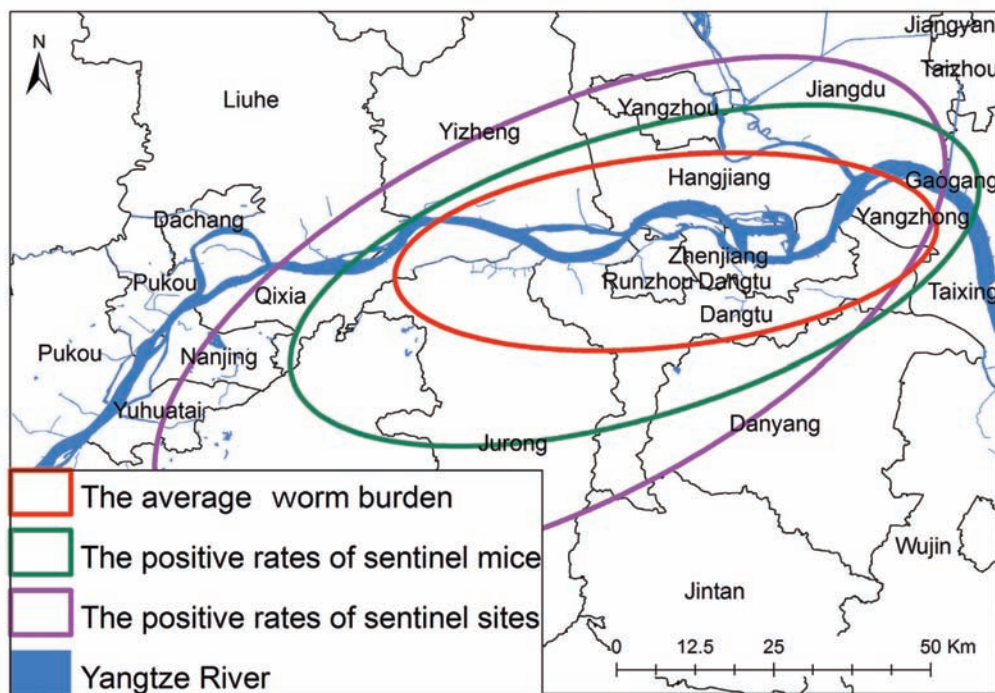


Fig. 5. The overall directional distribution of the positive rates of mice in sentinel sites and the average worm burden.

identify potential populations and factors of interest for further investigation (Wu et al., 2007; Yang et al., 2008; Malone et al., 2010). The studies referred to above were carried out in areas at medium to high levels of endemicity, while we were primarily interested in particularly low levels of endemicity. Indeed, the spatio-temporal analysis of the mouse bioassay data made it possible to identify the level of risk not only with regard to time and location but, importantly, also to do so in situations characterised by an extremely low-level of endemicity.

The comparatively high numbers of mice used in the different years were needed because of the very long stretch of the Yangtze River and to the high number of people living along its edges. This need was further strengthened due to the fact that the success of the control programme had already suppressed the infection levels both in humans and livestock below 1% in Jiangsu province making infections difficult to find (Hong et al., 2011; Sun et al., 2011, 2012).

Taken together, the investigations described here showed significant differences between the positive rates of surveillance sites and sentinel mice in different months and years already at the descriptive level of analysis. The positive rates were the highest in the project carried out in 2009 and decreasing gradually over the 3 years covered to reach the lowest levels in 2011. This development can be explained by the strengthening of snail control with niclosamide that

took place in the high-risk regions (Wang et al., 2009; Yang et al., 2010). In contrast, however, the average worm burden increased from 2.3 to 4.0 during the whole 3-year period indicating that infection transmission intensity remained serious in some areas.

The SDE approach has many applications. For example, mapping the distributional trend for a certain type of crime might identify a relationship with particular features, e.g. a string of bars or restaurants (Scott and Janikas, 2010). It can also visualise the degree of various distribution dispersions (Yuill, 1971; Khan, 1986; Gong, 2002; Tenzin et al., 2010) and provide applications for how disease outbreaks spread (Mitchell, 2005). In our studies, three parameters were used to describe and define the standard deviational ellipse, namely the angle of rotation for the distribution direction and the deviations along the long and the short axis for the degree of dispersion. As Fig. 4 shows, the spatial distribution patterns of the positive rates at the sentinel sites, the mice and the worm burdens were similar. In addition, the orientation of the ellipses along the Yangtze River indicated very clearly that the river was the focus of risk. Both the long and the short axis decreased significantly between 2009 and 2011, presenting increasingly compact ellipses over time with the main risk concentrated in Dangtu county. The results confirm that schistosomiasis transmission has been significantly reduced in Jiangsu province since the implementation of the long-term control plan by the provin-

Table 3. Significant clusters found by the SaTScan for the positive sentinel mice in the study area.

Year	Month	County	Cluster location	Cluster radius (km)	Relative risk (RR)	P-value
2009	May	Dantu	32.236 N and 119.379 E	0	3.13	0.050
	June	Liuhe	32.190 N and 118.950 E	11.73	11.50	0.050
	August	Hangjiang	32.245 N and 119.360 E	0	4.60	0.022
	September	Yangzhong	32.290 N and 119.730 E	4.29	1.53	0.050
2010	June	Dantu	32.224 N and 119.363 E	0	2.00	0.011
2011	August	Dantu	32.235 N and 119.481 E	0	2.00	0.011

cial government, especially after 2009. Fig. 5 shows that both the worm burden axes were shorter than the positive rates of sentinel mice and sites, which indicates the deviation of transmission intensity was lower. It also tells us that the transmission intensity, although previously very high, decreased over the 3 years. The possibility that transmission was tempered not long ago and could have left occasional definite hosts (livestock or humans) with a high worm burden is the most probable explanation for the unexpected increase of the average worm burden detected in the infected mice in 2011.

The SaTScan™ method has become an increasingly popular adjunct for exploring the spatio-temporal distribution of infectious diseases (Kulldorff, 2001; Kulldorff et al., 2005; Higgs et al., 2007), and more and more studies in P.R. China use it to confirm clus-

ter results with respect to schistosomiasis and to further explore disease patterns (Zhang et al., 2008; Li et al., 2009). We used scan statistics to identify the spatio-temporal clusters finding four significant such clusters in 2009 with high numbers of positive sentinel mice, but only one in 2011 (located in Dantu county). This particular high risk is best explained by the environmental setting. First, the geographical location of the cluster was on an island in the Yangtze River with a high density of snails and a large area of snail habitats (Zhou et al., 2001; Dai et al., 2011). Second, a small ferry connects the island with the mainland, contributing to a stronger activity of mobile people resulting in more people at risk (Wu et al., 1993; Steinmann et al., 2006). Third, available local, control resources were insufficient (Utzinger et al., 2005; Zhou et al., 2005). After the revelation of this remaining cluster in

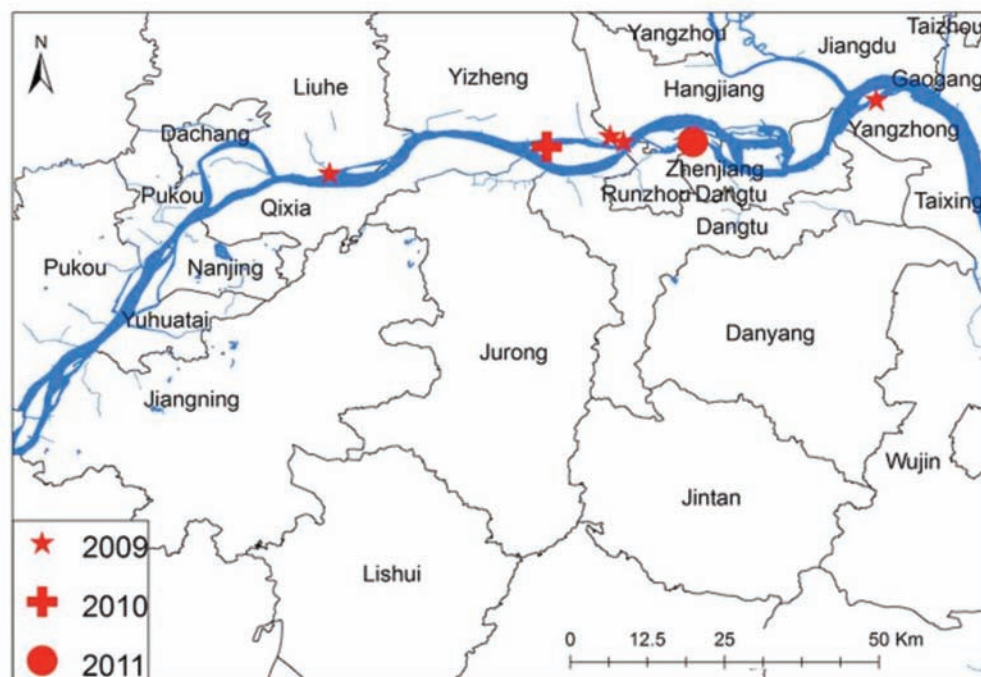


Fig. 6. Significant clusters of positive sentinel mice.

Dantu, more health resources assigned to this area resulting in the interruption of schistosomiasis transmission also in this area. However, although the approach described here was successful, the spatial distribution of schistosomiasis may be multifactorial and accuracy of the model might need to be further improved.

The discovery of two infection peaks in the study region, already apparent in the descriptive analysis, was confirmed by Scan statistics that showed that there were temporal clusters both in June and September. This two-peak transmission pattern is consistent with previous reports and can be explained by the evolvement of the snail populations and the length of the schistosome life cycle in P.R. China (Zhang et al., 1990; Wilke et al., 2000; Zhou et al., 2011). It means that cercariae were first shed from infected snails around June and infecting their definitive hosts around this time, providing the time needed to mature into worms and complete their life cycle resulting in a new generation of infected snails beginning the shedding cycle in September.

Conclusions

The development of better assessment for infection risk has become critical with improved control efforts continuously decreasing schistosomiasis transmission levels. The projection of surveillance replacing active control requires that an optimal approach, an EWS as it were, is in place. The creation of an investigative framework, capable of identifying risk through an integrated approach, should assist in designing evidence-based control strategies to be applied in the process of schistosomiasis elimination in P.R. China (Zhou et al. 2013).

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