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The emergence of angiostrongyliasis in the People's Republic of China: the interplay between invasive snails, climate change and transmission dynamics

SHAN LV[*,†,‡], YI ZHANG[‡], PETER STEINMANN[*,†,‡], GUO-JING YANG[§], KUN YANG[§], XIAO-NONG ZHOU[‡] AND JÜRG UTZINGER[*,†]

[*]*Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland*
[†]*University of Basel, Basel, Switzerland*
[‡]*National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, Shanghai, China*
[§]*Jiangsu Institute of Parasitic Diseases, Wuxi, China*

SUMMARY

1. Only few freshwater snail species transmit the rat lungworm *Angiostrongylus cantonensis*, which is partially explained by the low likelihood of contact between snails and infected rat faeces. The snail *Pomacea canaliculata* was introduced into China in 1981 and has become the key intermediate host for *A. cantonensis*. Thus far, the snail has been recorded in 13 provinces of southern China.
2. We developed a biological model and assessed potential impacts of climate change on the distribution of *P. canaliculata* and hence the transmission of *A. cantonensis*. Mean January temperature and snail generation intensity (generation number) were identified as the key factors determining *P. canaliculata* distribution. Our models predict an increase of 56.9% for the 'spread' and a decrease of 40.9% for the 'establishment' regions ('spread' and 'establishment' defined according to a national sampling survey) by the 2030s relative to the present day.
3. Key determinants of *A. cantonensis* transmission were identified as the generation intensity in the intermediate host, the longevity of *A. cantonensis*-infected rats and the dormant period of *P. canaliculata*. Transmission of *A. cantonensis* occurs only in areas where the snail's dormant period is <173.2 days. The potential endemic area of *A. cantonensis* is predicted to double by the 2030s relative to the present day.
4. The tight fit of our model predictions with data derived from a national sampling survey suggests that biological models hold promise for assessing potential impacts of climate change on infectious diseases once key determinants have been established. Geographical variation analysis may offer an approach to identify areas prone to the spread of vectors, intermediate hosts and parasites in a future warmer China and elsewhere.

Keywords: *Angiostrongylus cantonensis*, climate change, invasive snail, *Pomacea canaliculata*, vulnerable area

Introduction

Angiostrongylus cantonensis (Chen, 1935) (Nematoda: Metastrongylidae) is also known as 'rat lungworm', since adult worms parasitise the pulmonary arteries of rats. Molluscs, e.g. freshwater and terrestrial snails,

Correspondence: Shan Lv, Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, PO Box, CH-4002 Basel, Switzerland.
E-mail: lvshan000@126.com

serve as the intermediate hosts. In the human body, the worms usually fail to enter the pulmonary arterial system through the central nervous system (CNS) as they do in rats, and instead lodge in the human CNS where they induce inflammation characterised by elevated eosinophil counts in the cerebrospinal fluid (Lv *et al.*, 2010).

Eosinophilic meningitis because of an infection with *A. cantonensis* is endemic in South-east Asia, the Pacific Islands and the Caribbean (Wang *et al.*, 2008; Lv *et al.*, 2010). Humans acquire an infection through the consumption of undercooked snails, slugs and paratenic hosts (e.g. crabs, frogs and lizards), as well as contaminated vegetables. Only a few freshwater snail species are known to be involved in the natural transmission of angiostrongyliasis, most prominently *Pomacea canaliculata* (Lamarck, 1822) (Gastropoda: Ampullariidae), although many other snails have been demonstrated to be susceptible to *A. cantonensis* in experiments (Chang, Cross & Chen, 1968; Yousif & Lammler, 1975; Lv *et al.*, 2006a). A recent review of published human angiostrongyliasis cases from the mainland of China suggests that three-quarters of the 334 cases reported before 2006 were directly related to the consumption of *P. canaliculata*. The first parasitologically diagnosed case report dates back to 1984, and the first recognised outbreak occurred in 1997 (Lv *et al.*, 2008). Since then, the number of cases has steadily increased. Six of seven outbreaks involving more than five individuals could be attributed to the consumption of *P. canaliculata* (Lv *et al.*, 2008). Two recent outbreaks in 2007 and 2008 were also attributed to this snail species (Deng *et al.*, 2007; Lv *et al.*, 2009a). The first national survey of *A. cantonensis* in China showed that *P. canaliculata* is widely distributed in the southern part of the country (Lv *et al.*, 2009b). Hence, there is growing evidence that eosinophilic meningitis as a result of *A. cantonensis* infection is emerging in China.

The emergence of angiostrongyliasis has largely been attributed to the spread of *P. canaliculata*. Compared with other snail species, *P. canaliculata* displays a number of unusual biological features. It is amphibious, usually inhabiting slow-moving or stagnant waters such as shallow swamps, marshes, ditches, lakes and rivers, but is also able to survive outside freshwater bodies by breathing air, especially during oviposition (Joshi & Sebastian, 2006). The latter trait is significant as it enhances the chance for contacts between snails and rat faeces and hence the risk of infection with *A. cantonensis*.

Pomacea canaliculata originates from South America and is the only freshwater snail listed among the global top 100 invasive species (Lowe *et al.*, 2000). Its current invasive range includes East Asia and North America (Joshi & Sebastian, 2006). In 1979, *P. canaliculata* was introduced from Argentina by commercial snail farms into Taiwan to be cultured indoors for human consumption and, subsequently, the snail spread through eastern Asia (Joshi & Sebastian, 2006). The current distribution includes the mainland of China, Japan, the Republic of Korea, the Philippines, Indonesia, Malaysia, Singapore, Vietnam, Cambodia, Lao People's Democratic Republic (Lao PDR), Thailand and Myanmar (Joshi & Sebastian, 2006). A genetic analysis of the *P. canaliculata* complex in East Asia identified four species, namely *P. canaliculata*, *P. insularum*, *P. scalaris* and *P. diffusa*, indicating multiple independent introduction events over the past decades (Hayes *et al.*, 2008).

Similar to other biological invasions (Jeschke & Strayer, 2005), the spread of *P. canaliculata* in eastern Asia underwent three phases, namely introduction, establishment and spread. The snail was originally intentionally introduced, but in tropical and subtropical areas, *P. canaliculata* rapidly found its way into the surroundings and spread via water networks after a short phase of establishment. A different pattern has been observed for temperate areas, e.g. in central and northern China, where the snail was commonly introduced for commercial purposes in the late 1980s and early 1990s (Wei, Hu & Zhou, 1985; Wang, 1988; Yang & Tang, 1992; Zhao *et al.*, 1992), but failed to establish in the wild. One of the most important factors driving the invasion of *P. canaliculata* is environmental temperature, although many other variables, such as the level of dissolved oxygen, the pH of the water and soil moisture during dormancy, are implicated in the success of overwintering (Ito, 2002). Environmental temperature not only determines the establishment of cold-blooded animals, including *P. canaliculata*, but also affects their reproductive rate and hence population dynamics.

Vectorborne diseases are generally expected to expand their range (Githeko *et al.*, 2000; Yang *et al.*, 2010) or shift geographically (Lafferty, 2009) as a result of climate change (i.e. human-induced rise in temperature). Here, we explore the interplay of invasive *P. canaliculata*, climate change and transmission dynamics of angiostrongyliasis. In a first step, we develop a biological model of *A. cantonensis* transmission with *P. canaliculata* considered as the only intermediate host using key parameters to fit the current distribution in China. Second, we assess potential impacts of climate change on the distribution of *P. canaliculata* and consider the transmission dynamics of angiostrongyliasis in a future, warmer China.

Methods

Current distribution of Pomacea canaliculata *and* Angiostrongylus cantonensis

Two data sources were used to delineate the current distribution of *P. canaliculata* and *A. cantonensis* in China. The first is the national random sampling survey of *A. cantonensis* and its intermediate hosts, carried out in China in 2006 and 2007 (Lv *et al*., 2009b). The surveyed areas had been determined based on the potential presence of *P. canaliculata*, i.e. where more than one generation per year could survive according to a degree-day model. A grid sampling strategy was employed to identify the survey sites, with their geographical coordinates recorded using hand-held global positioning system devices (GPSmap 70; Garmin International, Olathe, KS, U.S.A.). *Pomacea canaliculata* was collected from natural habitats near human settlements (e.g. ponds, crop fields and streams). Snails were examined for the presence of *A. cantonensis* using lung examination and artificial digestion (Lv *et al*., 2009b,c). Other snails, including *Achatina fulica* (Bowdich, 1822) (Gastropoda: Achatinidae) and terrestrial slugs were also collected and examined using artificial digestion. Rats were trapped and dissected for the presence of adult *A. cantonensis* in lung arteries and the heart. The results of this survey revealed that both *P. canaliculata* and *A. cantonensis* are widely endemic in southern China (Fig. 1).

The second source pertained to areas beyond the current distribution range of the snail identified by the national sampling survey (indicated with stars in Fig. 1). Specifically, we collected relevant information including snail species and exact location from Chinese newspapers and Internet-based reports published between January 2008 and December 2009.

Our assumption was that the current distribution of *P. canaliculata* in China reflects the maximum extent possible under prevailing environmental conditions. Two considerations support this assumption. First, *P. canaliculata* had been repeatedly introduced into China in the 1980s, but became established only in southern provinces. Second, the isolated population in the Sichuan basin was established in the late 1980s, but failed to expand to the middle or lower Yangtze River valley. It is important to note that 'establishment' areas, which include the distribution according to local reports, usually consist of isolated populations and hence are difficult to discover by a random sampling survey. The current distribution of *P. canaliculata* in China was therefore stratified into two regions: (i) the aforementioned 'establishment' area and (ii) the 'spread' area, which corresponds to the habitat where *P. canaliculata* snails were readily found during the national sampling survey.

Key transmission factors of Angiostrongylus cantonensis

The transmission of *A. cantonensis* is complex and involves two distinct phases: parasitism in a warm-blooded animal (i.e. rats) and in a cold-blooded animal (i.e. molluscs). Only the latter phase is markedly affected by environmental temperatures. Moreover, the transmission can involve other mollusc species whose roles in the transmission may be asymmetrical. For example, terrestrial slugs and snails may play a role in sustaining the life cycle of *A. cantonensis* in a particular location. Here, we consider only *P. canaliculata* because it is by far the most important snail species implicated in human infections in China (Lv *et al*., 2008). Moreover, this species can spread *A. cantonensis* over long distances via water networks and it occurs in larger habitats than, for example, *A. fulica*, another intermediate host snail found in China (Lv *et al*., 2009b).

We developed a biological model and considered several factors that relate to temperature, such as the population density of the snail intermediate host, the developmental period of *A. cantonensis* within *P. canaliculata* and the transmission season of *A. cantonensis* (Fig. 2). Since snail dormancy may occur, the longevity of infected rats and the parasite and the cold tolerance of snails and parasites were also taken into account. Parameters used in our model are summarised in Table 1 and further detailed later.

The first parameter pertains to the generation intensity of *P. canaliculata*, which is determined by

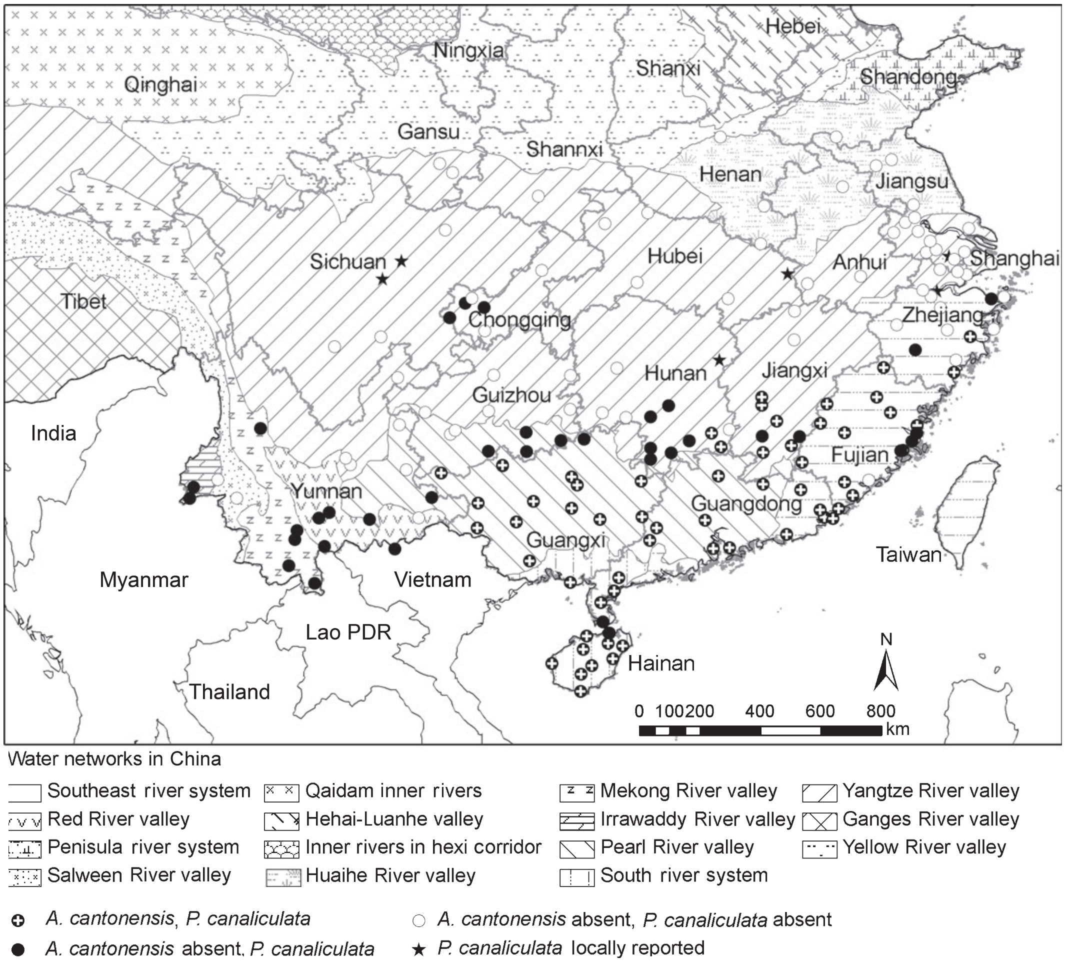

Fig. 1 Current distribution of *Pomacea canaliculata*, *Angiostrongylus cantonensis* and major river catchments in China.

the accumulated effective thermal energy (AET) and developmental threshold temperature (DTT). These two parameters are derived from empirical theory, which assumes that a plant or a poikilotherm animal develops only once the environmental temperature is higher than a specific minimal threshold, and that the total thermal energy required for this development is constant (Higley & Haskell, 2001). We used the parameters derived from the data of Zhou *et al.* (2003) to calculate the generation intensity of *P. canaliculata* (see eqn 1).

$$\mathrm{Gen} = \frac{\mathrm{AET}_y}{\mathrm{AET}_t} \tag{1}$$

'Gen' is the generation intensity (number of generations per year), AET_y is the yearly AET, and AET_t denotes the AET for one generation.

In our study, the lower limit of the generation intensity delimiting the potential range of *P. canaliculata* was fitted using the known distribution. First, we selected the point with the lowest generation intensity as the index point on the current distribution limits of the snails. The boundary was produced using the contour function of ArcGIS (version 9.1; ESRI, Redlands, CA, U.S.A.).

The second parameter considered is the developmental period of *A. cantonensis* within *P. canaliculata*. Of the five larval development stages, the first three (L_1–L_3) take place within the snail and hence are directly influenced by temperature. On the other hand, the fourth and fifth larval stages (L_4 and L_5), as well as adult worms, are barely affected by the environmental temperature, as they take place within rats. The period between L_3 larvae infecting rats and the emergence of L_1 larvae in rat faeces is 5–6 weeks,

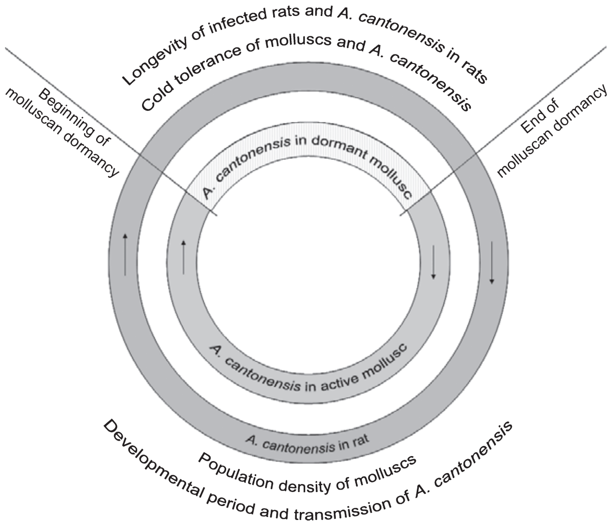

Fig. 2 Determinants of the transmission of *Angiostrongylus cantonensis*, with an emphasis on factors pertaining to environmental temperature. The two circles represent distinct phases in the life cycle of *A. cantonensis*.

but depends on worm burden (Kino, 1984). The DTT and AET for this phase have been determined in the laboratory under constant temperature (Lv *et al.*, 2006b). A linear equation based on a degree-day model was fitted in this experiment to describe the developmental period of *A. cantonensis*, with key parameters summarised in Table 1. The generation intensity within the intermediate host can be determined by eqn 1.

The third parameter relates to the transmission season of *A. cantonensis*. Transmission is on hold during the dormant period of the snail intermediate host. However, the transmission may be interrupted even during periods when snails are active if the development of *A. cantonensis* has not been triggered. Therefore, the DTT of *A. cantonensis*, determined at 15.04 °C, is a key factor considered in our model. The number of days with mean temperature above 15.04 °C has thus been retained in the model.

The fourth parameter considered is the cold tolerance of *P. canaliculata* and *A. cantonensis*. Reliable experimental data pertaining to cold tolerance of *P. canaliculata* are not available (Howells *et al.*, 2006). A field observation made in Japan found a linear relationship between winter (December–February) air temperature and mortality of *P. canaliculata* (Shobu *et al.*, 2002). The minimal threshold temperature for snail survival was estimated at 9.67 °C. However, a preliminary analysis using the winter temperature of December–February showed that the distribution of *P. canaliculata* in China stretched far beyond this 9.67 °C isotherm. Indeed, the present global distribution of the snail further indicates that populations can tolerate winter temperatures of 4–5 °C (Cazzaniga, 2006). Therefore, we used the current distribution of *P. canaliculata* in China to fit the potential range. First, we determined the mean January temperature (the lowest monthly temperature in China) of each endemic focus and selected the

Table 1 Parameters considered for modelling and predicting the transmission of *Angiostrongylus cantonensis* in China

Host/parasite	Determinant	Parameter	Values	Unit	Reference
Pomacea canaliculata	Generation intensity	DTT	11.67	°C	Zhou *et al.* (2003)
		AET	1404.1	Degree-day	Zhou *et al.* (2003)
	Cold tolerance	Low temperature for ‘spread’	5.43	°C	*
		Low temperature for ‘establishment’	3.62	°C	*
	Dormancy	Threshold temperature	17.0	°C	Yin *et al.* (2006)
Rat	Longevity of infected rats	Life span	173.2	Day	†
A. cantonensis	Generation intensity	DTT	15.04	°C	Lv *et al.* (2006b)
		AET	262.5	Degree-day	Lv *et al.* (2006b)
	Transmission season	Days above 15.04 °C	212	Day	*
	Cold tolerance	Low lethal temperature	–	°C	‡
	Longevity in rats	Life span	414.2	Day	Kino (1984)

AET, accumulated effective thermal energy; DTT, developmental threshold temperature.
*Fitted according to the current distributions.
†Obtained from a fitted function based on published data.
‡No specific data available, but cold tolerance of nematode considered equal or greater than that of their host, as supported by experiments.

location with the lowest value as an indication of the northernmost extent of 'spread' and 'establishment' regions and then produced the isolines using the contour function of ArcGIS.

We are not aware of data pertaining to cold tolerance of *A. cantonensis* within *P. canaliculata*. However, the cold tolerance of *A. cantonensis* within *A. fulica* has been assessed; the larvae were found to be alive and infective after snails had been kept at 0 °C for a period of 7 days (Alicata, 1967). Although the viability of the snails themselves had not been reported, many other experiments demonstrated that parasites have equal or greater cold tolerance than their hosts (Tyrrell *et al*., 1994; Woodhams *et al*., 2000; Smith, Wharton & Marshall, 2008). Hence, we assumed that the survival of *A. cantonensis* in low temperatures is equal to or higher than that of *P. canaliculata*.

The fifth parameter relates to the longevity of infected rats and *A. cantonensis* in rats. The leading definitive host is *Rattus norvegicus* (Berkenhout, 1769). Most of the trapped wild *A. cantonensis*-infected rats were infected with fewer than 30 adult worms, and the average number of worms (worm burden) carried by an individual rat reported in different publications ranged from 2 to 19.9. A few rats were found to be infected with up to 90 worms (Ding *et al*., 1982; Ye *et al*., 2007). Laboratory experiments demonstrated that heavily infected rats (>30 adult worms) usually died within 3 months (Kino, 1984; Liang, Shen & Li, 1984). We therefore concluded that the longevity of *A. cantonensis*-infected rats is associated with worm burden (Kino, 1984).

We fitted an exponential function relating longevity of *A. cantonensis*-infected rats and worm burden based on an adaptation of data derived from experiments conducted by Kino (1984). The literature on field surveys of rats infected with *A. cantonensis* in China was reviewed, and the average worm burden among wild rats determined as 11.3. The mean life span of infected rats was estimated at 173.2 days according to an exponential function and the average worm burden mentioned previously. We assumed that *A. cantonensis* transmission ceased if snails cannot ingest infective rat faeces for a period equal to or longer than the mean longevity of infected rats. The mean reproductive duration of the worms was estimated to be as long as 414.2 days in rats carrying two worms (one female and one male) (Kino, 1984). Therefore, the life span of *A. cantonensis* in rats does not influence the life cycle in case of dormancy of *P. canaliculata*.

The sixth and final parameter considered is the dormant period of *P. canaliculata*. A decrease in activity among intermediate host snails eventually interrupts the transmission of *A. cantonensis*. We defined dormancy as a significant decrease in snail activity from the perspective of *A. cantonensis* transmission. Under natural conditions, *P. canaliculata* becomes inactive and enters dormancy if the water temperature drops below 17 °C (Ito, 2002; Yin *et al*., 2006). In our study, we set the water temperature equal to the air temperature, because *P. canaliculata* usually lives in shallow water and is active close to the water surface where temperatures approximate those of the air. The number of days with mean temperatures below 17 °C was designated as the dormant period.

Climate data

Climate data, specifically daily minimum, mean and maximum temperatures at 740 observing stations across China, were obtained from the Chinese National Satellite Meteorological Center in Beijing. Stations with incomplete data were excluded from the analysis. For each station, the geographical coordinates were assigned and the temperature at locations between observing stations was estimated using ordinary kriging. This geostatistical technique is used to infer a value for non-surveyed location based on observed values in neighbouring points. Temperature data spanning one decade (i.e. 1991–2000) were employed for analysing the distributions of *P. canaliculata* and *A. cantonensis*.

The predicted temperature data from 1991 to 2100 were derived from the PRECIS model [PRECIS stands for 'Providing Regional Climates for Impacts Studies', which downscaled the U.K. Hadley Centre Atmospheric Model (HadAM3), based on the 'Special Report on Emissions Scenarios' (SRES) A2 (Nakicenovic *et al*., 2000)]. The spatial resolution of the data set is 50 × 50 km, contains more than 10 000 grid points with daily mean temperatures at the respective grid points and covers the entire area of China. In the PRECIS model, the climate data for the period 1961–1990 were considered as the baseline. The 2020s (2021–2030) and 2030s (2031–2040) were selected as the target decades for predicting the distributions of *P. canaliculata* and *A. cantonensis*.

To explore whether the predicted data were accurate, we compared the real temperature data observed between 1991 and 2000 with the predicted data for the same period. We first used the predicted average annual temperature to generate a smooth prediction map of China using a geographical information system (GIS) platform and then extracted the values at the corresponding observing stations. The difference was estimated for each station by comparing real data with those predicted by the model. The difference was employed to produce another smooth map, and the corresponding values were extracted. Finally, the adjusted daily temperature values were obtained by adding the differences to the predicted daily temperature.

Modelling and mapping in a GIS platform

We used ordinary kriging as an interpolator to predict values at non-sampled locations, employing a GIS established in ArcMap. Data, including the generation intensity for snails and parasites and dormant periods, were transformed to achieve normal distributions using a square-root transformation. Kriging models with different orders were compared using standard tools for comparison, and the best-fitting model was selected. Surface analysis (i.e. the contour function) was employed to produce isolines of the mean January temperature, generation intensity and snail dormant period.

The potential range of *P. canaliculata* was determined by superpositioning the respective areas determined by the lower limit of the generation intensity and cold tolerance of the snail. The distribution of *A. cantonensis* was determined using a combination of several factors with details provided in Table 1. The at-risk areas for transmission of *A. cantonensis* were predicted for the 2020s and 2030s.

We defined 'vulnerable areas' as regions where a small change [e.g. one standard deviation (SD)] of a climatic factor (e.g. mean January temperature) or a biological factor (e.g. snail dormant period) would tip the status of the region, e.g. from 'establishment' to 'spread'. To identify the 'vulnerable areas', we assessed the annual geographical variation of the mean January temperature and dormant period of *P. canaliculata*. For each observing station or grid point, we used the average plus one SD as the upper value and the average minus one SD as the minimum extent, and then generated prediction maps, employing ordinary kriging. The same isolines were identified in all maps, and the region between them was considered the vulnerable area.

Results

Current distribution of Pomacea canaliculata *in China, including uncertainty*

A total of 98 endemic foci were identified during the national sampling survey (Fig. 1), and the area where they were found was consequently classified as 'spread' regions. Among them, Dali in the northern part of Yunnan province showed the lowest annual thermal energy for the development of *P. canaliculata*, allowing only 1.12 (indicated as square root, i.e. 1.06 in Fig. 3a) generations per year. The 'establishment' region was determined based on six isolated populations identified from local reports. Of these, Dayi on the western edge of the Sichuan basin had the lowest annual thermal energy, allowing only 1.09 (square root 1.04 in Fig. 3a) generations per year. Areas characterised by more than 1.12 or 1.09 generations, respectively, consist of two major parts: the first is in south-east China and the second in the desert area of Xinjiang province in the north-west of the country.

With a mean January temperature of 5.43 °C, Jiangdong in eastern Zhejiang province had the lowest temperature among all endemic foci in the 'spread' region. Yingshan in eastern Hubei province had the lowest mean January temperature (3.62 °C) among the six foci in the 'establishment' region. Considering these isotherms and generation contours, we predicted that *P. canaliculata* can only become firmly established in the south-eastern part of the country (Fig. 3a). Our data suggest that compared with the annual thermal energy required for the development of *P. canaliculata* (more than one generation per year), cold tolerance is the crucial factor determining its distribution.

The 'spread' region covers the provinces of Guangdong, Hainan and Fujian and Guangxi Zhuang autonomous region, as well as the southern parts of Yunnan, Guizhou, Hunan, Jiangxi and Zhejiang provinces. Isolated areas occur in the eastern part of Sichuan province and the western part of Chongqing municipality. The 'establishment' region mainly consists of the northern parts of Guizhou, Hunan, Jiangxi

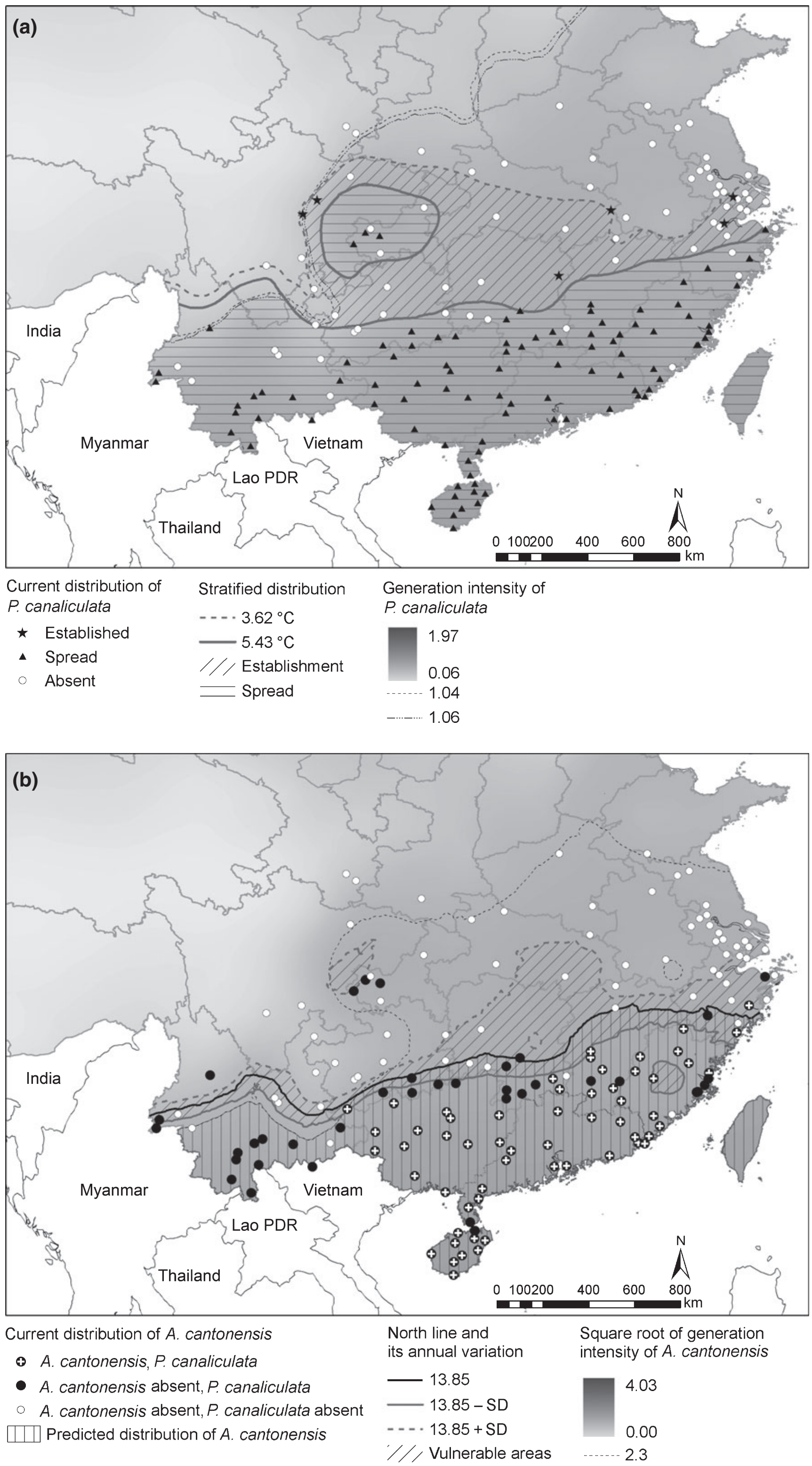

Fig. 3 (a) Current distribution of *Pomacea canaliculata* in China. The distribution is stratified into 'spread' and 'establishment' regions. (b) Current distribution of *Angiostrongylus cantonensis* in China. Coexistence of *A. cantonensis* and *P. canaliculata* at each sampled site is shown in three groups; 13.85 denotes the square root of 191.8 days, which is the limit active period of *P. canaliculata*.

and Zhejiang provinces, as well as southern Hubei and Jiangsu provinces. Shanghai municipality and the eastern parts of Sichuan province and Chongqing municipality also form part of the 'establishment' area. The areas of the 'spread' and 'establishment' regions were 1 217 434 and 554 658 km^2, respectively (Table 2).

The locations of the 5.43 and 3.62 °C mean January isotherms varied considerably between 1991 and 2000 (Fig. 4). In the 'spread' region, the geographical variation was considerable between the isotherm of 5.43 °C and the line of 5.43 °C + 1 SD, particularly in the central area, while only a slight parallel change was found between the average line and the line of 5.43 °C − 1 SD. The main variation was observed in the eastern part of the country. A major overlap of variations was observed in both regions, indicating wide fluctuations in winter temperatures during the period 1991–2000.

Potential change in the distribution of Pomacea canaliculata *in the 2020s and 2030s*

According to our predictions, the 'establishment' region will decrease and move north-eastwards by the 2020s and 2030s (Figs 5a & 6a). However, the 'spread' region will significantly expand and include almost the whole current 'establishment' region by the 2030s. Taking into consideration both generation intensity and cold tolerance of *P. canaliculata*, an estimated net increase of 314 376 km^2 of the 'spread' region and a decrease of 101 705 km^2 of the 'establishment' region is predicted for the 2020s. A major increase in the 'spread' region is predicted to occur near the boundary between Hunan, Jiangxi and Hubei provinces (Fig. 5a). In addition to a decrease in the surface area, the 'establishment' region is predicted to move north-east, involving the central part of Anhui province and the southern part of Jiangsu province.

Our predictions suggest that the 'spread' region will have further expanded northwards by the 2030s. Almost the entire Chongqing municipality as well as Hunan, Hubei, Jiangxi and Zhejiang provinces will become 'spread' areas (Fig. 6a). The predicted increase in the surface area of the 'spread' region between the 2020s and 2030s is 378 700 km^2. The 'establishment' region will further move north-east, mainly including the Huaihe River valley in southern Henan and Anhui provinces, and central Jiangsu province. The decrease in the 'establishment' region between the 2020s and the 2030s is predicted at 125 102 km^2.

The potential impact of climate change on Angiostrongylus cantonensis *transmission*

The parameters considered in our biological model for assessing the distribution of *A. cantonensis* include (i) the thermal requirement for the development of the parasite in the snail intermediate host (generation intensity), (ii) the dormant period of *P. canaliculata*, (iii) the longevity of *A. cantonensis*-infected rats, (iv) the longevity of the parasite in rats, (v) the transmission season, and (vi) the cold tolerance of the parasite within the snail. In a first step, each parameter was used in our model and the predicted distribution of *A. cantonensis* was compared with the real distribution. Since the latter three parameters resulted in less meaningful predictions (i.e. the predicted ranges were far beyond the real distribution) than the former three, they were excluded from the final model.

Table 2 Current and predicted distribution range of *Pomacea canaliculata* and *Angiostrongylus cantonensis* in China

	At present	2020s (2021–2030)		2030s (2031–2040)	
Region name	Area (km^2)	Area (km^2)	Change (km^2)*	Area (km^2)	Change (km^2)*
'Spread' region of *P. canaliculata*	1 217 434	1 531 810	314 376	1 910 510	693 076
'Establishment' region of *P. canaliculata*	554 658	452 908	−101 705	327 806	−226 807
Endemic area of *A. cantonensis*	881 735	1 494 014†	612 279	2 199 694‡	1 317 959
Overlap§	874 690	1 311 943	437 253	1 697 181	822 491

*Increment compared with present situation.
†Including 24 188 km^2 in desert area in central part of Xinjiang Uyghur autonomous region.
‡Including 238 364 km^2 desert area in the central part of Xinjiang Uyghur autonomous region.
§Between endemic area of *A. cantonensis* and 'spread' region of *P. canaliculata*.

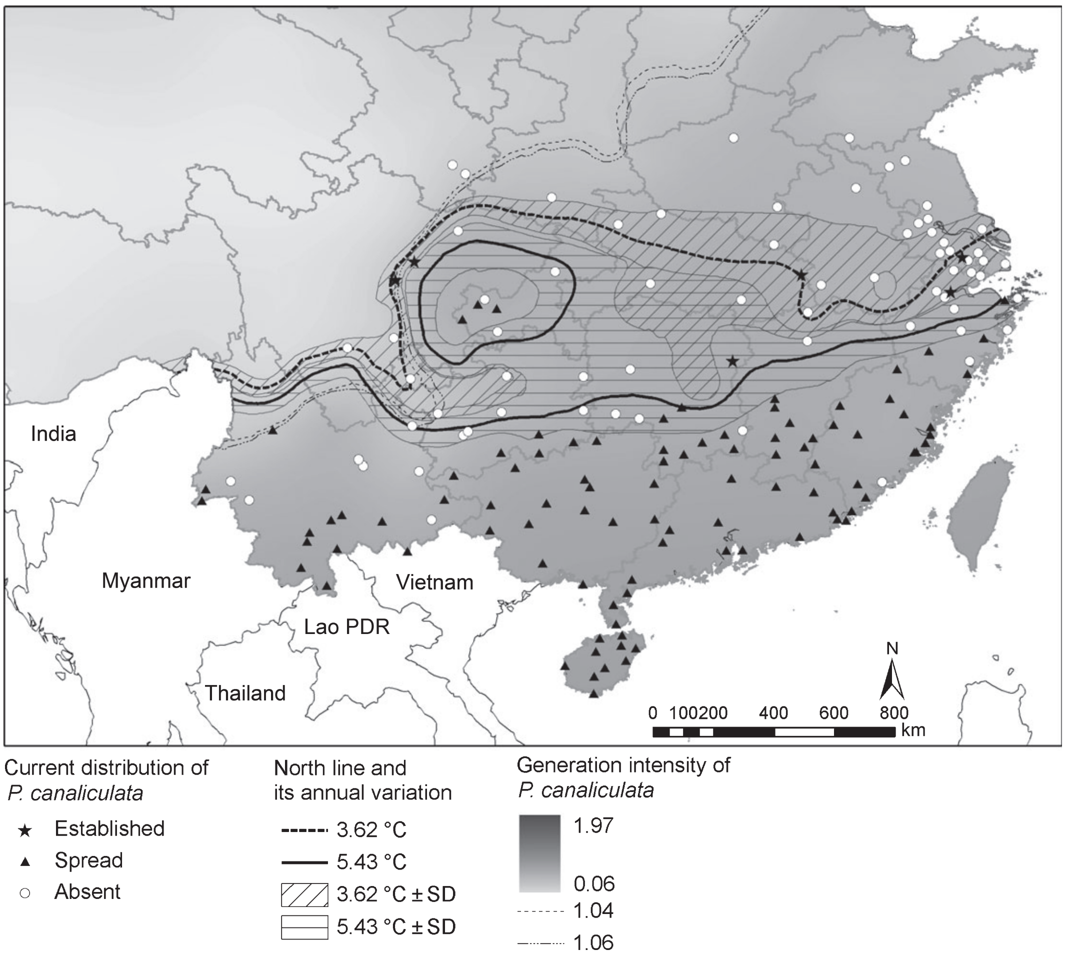

Fig. 4 Annual variation of the northernmost limit of the 'spread' and 'establishment' regions of *Pomacea canaliculata* in China. The thick lines describe the average extent of each region in the 1990s.

The generation intensity of 5.29 (square root 2.30; see Figs 3b, 5b & 6b) reflects the least stringent thermal requirements for parasite survival according to the current distribution of *A. cantonensis*, but is not the key factor to determine the range of *A. cantonensis* (Figs 3b, 5b & 6b). Given that 17 °C is the threshold temperature for inducing winter dormancy in *P. canaliculata*, the potential *A. cantonensis*-endemic area is where the dormant period is <173.2 days, or the active period is more than 191.8 days (square root 13.85; see Figs 3b, 5b & 6b) according to the longevity of *A. cantonensis*-infected rats with an average worm burden of 11.3 per rat. The predicted range of *A. cantonensis* matches the one currently observed, except for Yunnan province. The isoline of 191.8 days shows considerable variation between 1991 and 2000, especially in central and eastern China, including Hunan, Hubei, Jiangxi and Zhejiang provinces.

Considering a minimal generation intensity of 5.29 for *A. cantonensis* and an active period for *P. canaliculata* of 191.8 days, the current surface area where transmission of *A. cantonensis* can occur is 881 735 km^2. According to our model, the potential transmission area for *A. cantonensis* will significantly expand by the 2020s (Fig. 5b) and the 2030s (Fig. 6b). Compared with the present situation, the increase will be 612 279 and 1 317 959 km^2, respectively. Variation analysis of the 13.85 line (square root of 191.8 days) revealed considerable spatial heterogeneity. At present, the variable area mainly lies in the central part, while the area is predicted to shift north-east in the 2020s and the 2030s.

The endemic area of *A. cantonensis* shows a parallel increase to that of *P. canaliculata*, especially in the central and eastern parts of China. An increase in the south-western part is also observed. The overlap area

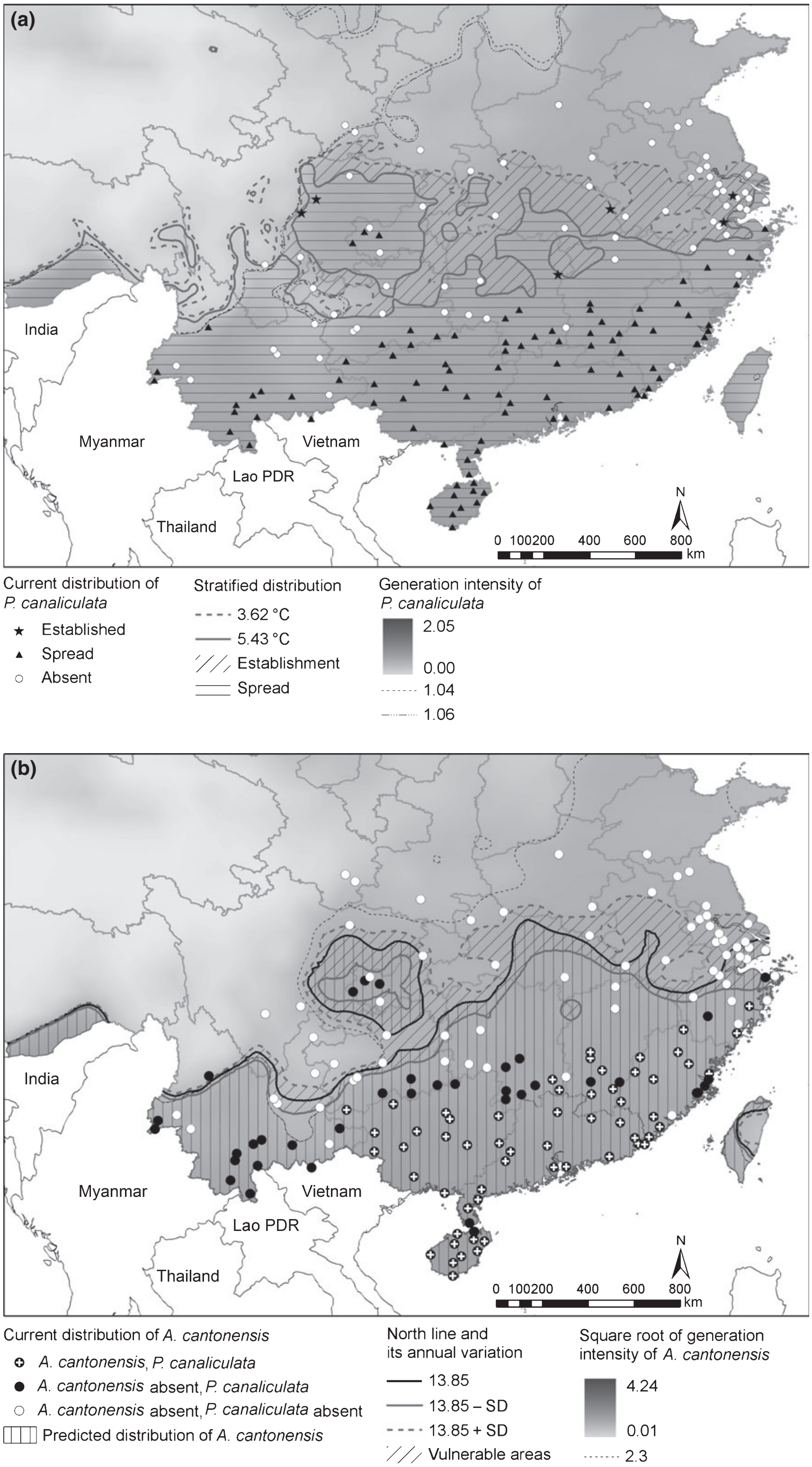

Fig. 5 (a) The potential distribution of *Pomacea canaliculata* in China in the 2020s. The distribution is stratified into 'spread' and 'establishment' regions. (b) The potential distribution of *Angiostrongylus cantonensis* in China in the 2020s. Coexistence of *A. cantonensis* and *P. canaliculata* at each sampled site is shown in three groups; 13.85 denotes the square root of 191.8 days, which is the limit active period of *P. canaliculata*.

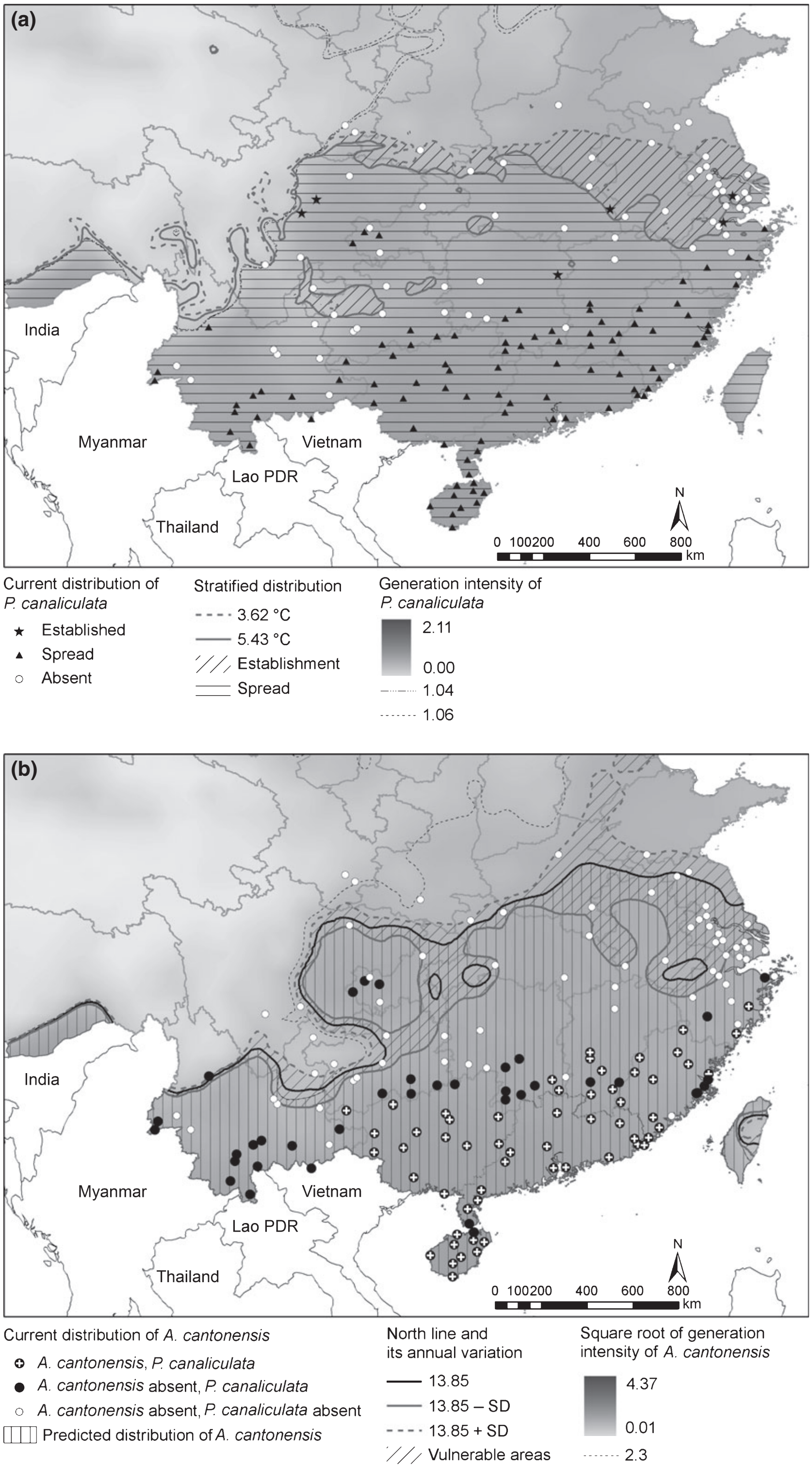

Fig. 6 (a) The potential distribution of *Pomacea canaliculata* in China in the 2030s. The distribution is stratified into 'spread' region and 'establishment' region. (b) The potential distribution of *Angiostrongylus cantonensis* in China in the 2030s. Coexistence of *A. cantonensis* and *P. canaliculata* at each sampled site is shown in three groups; 13.85 denotes the square root of 191.8 days, which is the limit active period of *P. canaliculata*.

between the predicted endemic area of *A. cantonensis* and the potential distribution of *P. canaliculata* is estimated to double by the 2030s compared with the present situation. Meanwhile, the fraction of this overlap accounting for *A. cantonensis*-endemic area is predicted to decrease from 99.2% at present to 87.8% in the 2020s and 77.2% in the 2030s.

Discussion

We have established a biological model to deepen our understanding of the transmission of *A. cantonensis* in China, including the role of an invasive snail species. The key features considered in the model consisted of the thermal requirement for the development of the parasite and the intermediate host snail, the dormant period of *P. canaliculata* and the longevity of *A. cantonensis*-infected rats. Importantly, our biological model facilitated appraisal of a potential impact of climate change; hence, we generated predictive risk maps for the distribution of *A. cantonensis* and *P. canaliculata* in a warmer future. Our predictions suggest that the *A. cantonensis*-endemic area will expand considerably along with a further spread of *P. canaliculata*. Our results raise several issues relevant to parasite–host interactions in the context of climate change, which we offer for discussion.

Emerging infectious diseases driven by invasive species and climate change

Many factors are involved in the emergence of infectious diseases (Morse, 1995; Morens, Folkers & Fauci, 2004). Among them, biological invasion is a central concern (Daszak, Cunningham & Hyatt, 2000; Juliano & Lounibos, 2005; Enserink, 2007; Poulin *et al.*, 2010). According to Mooney & Hobbs (2000), climate change is expected to exacerbate the invasion of exotic species, including vectors and intermediate hosts of pathogens. Indeed, an invasive freshwater snail species, i.e. *P. canaliculata*, has been identified as the major source of human angiostrongyliasis and a leading intermediate host of *A. cantonensis* in China (Lv *et al.*, 2008, 2009b, 2010; Yang *et al.*, 2010). Our results now suggest that the distribution of this invasive snail is likely to further expand in the face of climate change. Compared with the present situation, the predicted 'spread' area of *P. canaliculata* will increase by 25.8% in the 2020s and 56.9% in the 2030s. Most of this increase is predicted for the Yangtze River valley, the largest freshwater network in the country (Fu *et al.*, \2003). The predicted expansion of *P. canaliculata* will potentially drive the current *A. cantonensis*-endemic area further north. Major water resources developments, particularly the south-to-north water transfer project, might further fuel the spread of *P. canaliculata*, similar to the spread of *Oncomelania hupensis*, the intermediate host snail of *Schistosoma japonicum* (Yang *et al.*, 2005, 2010; Zhou *et al.*, 2008).

In our study, the overlap between potential distribution ranges of *P. canaliculata* and *A. cantonensis* was used to illustrate the role of this snail in the transmission dynamics of the parasite. The results show that the fraction of this overlap in the whole endemic area of *A. cantonensis* will decline, which indicates that the parasite will expand more rapidly than the intermediate host snail. In China, *A. fulica* is another snail species implicated in the transmission of *A. cantonensis* (Lv *et al.*, 2009b), and hence, the overlap region depicted in our prediction map might be an underestimation of the real future scenario. Despite this shortcoming, our model predicts that the endemic area of *A. cantonensis* will double, when comparing the present situation with that of the 2030s. Hence, the interplay of invasive snail species and climate change is likely to drive the endemicity of *A. cantonensis*, which is of considerable public health relevance.

In addition to the role of transmission, the further spread of *P. canaliculata* may facilitate the establishment of new transmission patterns. Previous field-based research suggests that the *A. cantonensis* infection intensity among terrestrial snails and slugs is significantly higher than that among freshwater snails including *P. canaliculata* (Li *et al.*, 2006; Hu *et al.*, 2007; Zhang *et al.*, 2007; Deng *et al.*, 2008). A possible explanation is that freshwater snails usually are exposed to lower concentrations of *A. cantonensis* L_1 larvae because rat faeces are diluted once they reach freshwater bodies. In case that *P. canaliculata* becomes the dominant intermediate host in the area where *A. cantonensis* transmission is likely to occur, it is conceivable that the infection pressure will decrease, resulting in lighter infections in wild rat populations and hence a prolonged life span of infected rats compared with the current situation. A new parasite–host equilibrium might then be established when this interaction pattern between *A. cantonensis* and *P. canaliculata* shifts from the original endemic areas where terrestrial slugs and snails were abundant.

Transmission dynamics of parasites from a biological and ecological perspective

A complex life cycle calls for a detailed biological model to describe the transmission dynamics. Unlike their vectors or intermediate hosts, parasites often are not directly exposed to environmental factors. Some parasites also have to switch their hosts to accomplish their life cycle. Different hosts do not necessarily share the same spatial distribution and ecological requirements and hence exert asymmetrical roles in the life cycle and transmission of parasites. The transmission of *A. cantonensis* can serve as an example. While several freshwater snail species are susceptible to this nematode (Chang *et al.*, 1968; Yousif & Lammler, 1975; Lv *et al.*, 2006a), natural infections are rare (Lv *et al.*, 2009b). An explanation is that most of these snails live in deep or fast-flowing water, and thus, contact with rat faeces is unlikely to occur. *R. norvegicus*, the most common definitive host of *A. cantonensis* (Lv *et al.*, 2008), mainly inhabits human settlements. As a result, the mollusc infection rate and worm burden in close proximity to human habitations are significantly higher than further away (Li *et al.*, 2006).

The longevity of vectors or intermediate hosts is an important factor to sustain the life cycle of parasites. For example, *Plasmodium* (the causative agent of malaria) have to accomplish their development within female *Anopheles* mosquitoes before the vectors die (Rogers & Randolph, 2000). In our study, the longevity of *P. canaliculata* is not considered since these snails usually live more than 1 year under suitable conditions (Cazzaniga, 2006) and are rarely influenced by infection (Lv *et al.*, 2006a). In contrast, the life expectancy of *A. cantonensis*-infected definitive hosts (i.e. rats) is significantly affected by their worm burden (Kino, 1984). We have explicitly taken this issue into account in our model, after reviewing available data and determining the relationship between worm burden and rat longevity. This consideration brings to the fore another ecological issue, namely the dormant period of molluscs, which is closely associated with environmental temperature. Our biological model considering the two aspects indeed shows a better fit to the real distribution of *A. cantonensis* than the parasite generation intensity alone.

Asymmetrical effects of climate change on different components of parasite–host models may also influence parasite transmission dynamics. Parasites and hosts may respond to climate change in different ways. Under a scenario of rising temperatures, the development of parasites and hosts may often be accelerated, but at different rates, because of specific energetic efficiency and metabolic rates (Paull & Johnson, 2011). In our study, DTT and AET differ between *A. cantonensis* and *P. canaliculata*, as manifested in different shifts in the distribution resulting from the same temperature change. Additionally, our results suggest that winter temperatures considerably affect the distribution of *P. canaliculata*, while transmission of *A. cantonensis* is driven mainly by the dormant period of molluscs and virulence in the rat definitive host. Appraisal of a potential impact of climate change on vectorborne diseases should therefore consider an ecological perspective.

Vulnerable area to climate change

Invasive species typically go through three phases: introduction, establishment and spread (Jeschke & Strayer, 2005). For the establishment and spread phases, a growing population is required (Arim *et al.*, 2006). Many environmental factors such as temperature can influence the growth of a population (Crooks & Soule, 2001). Sub-optimal temperature may result in a lag in the population growth and hence interrupt further spread. Rising temperatures may change the vulnerable area to a spread region.

Annual variation of the mean January temperature accounts for the current distribution of *P. canaliculata* in China. January temperatures are highly variable from one year to another as is evident from the large area between the isotherms of the average temperature and ± 1 SD. In the 'establishment' region, the isotherms showed dramatic shifts between subsequent years in the 1990s. The unstable temperature probably results in a high interannual variation in *P. canaliculata* population sizes and hence does not provide an environment for stable growth, which is a prerequisite for expansion. In contrast, temperatures in the 'spread' region are more stable and suitable for *P. canaliculata* as suggested by an isotherm of 5.43 °C − 1 SD, which is close to the 5.43 °C isotherm. The climate data based on SRES A2 suggest a significant increase in winter temperatures by the

2030s. Thus, the 'establishment' areas will become part of the 'spread' region.

We also analysed the variation in the dormant period of *P. canaliculata*, which is relevant to the transmission of *A. cantonensis*. The results show that there is considerable variation between the line of 13.85 and that of 13.85 − 1 SD, especially in the central part. This vulnerable area probably becomes *A. cantonensis*-endemic if the dormant period falls below 173.2 days along with rising temperatures. Our findings for the 2020s and 2030s underscore this issue.

In this study, the current distribution of *P. canaliculata* and *A. cantonensis* was fitted using a model built around key biological determinants and environmental temperature. The model was then used to assess a potential impact of climate change on the transmission dynamics of *A. cantonensis*. The most important finding of our investigation is that, in the face of climate change, the distribution of an invasive freshwater snail species will change and hence exacerbate the endemicity of *A. cantonensis*. Our study also suggests that geographical variation analysis is a useful tool to identify areas that are most vulnerable to the spread of intermediate hosts and might also be applicable for vectors and parasites.

The present study calls for rigorous surveillance and identified two major research needs. With regard to surveillance, a precise knowledge of the actual distributions of the snail and the parasite is needed for further model refinement. Indeed, our findings show that the predicted range of *P. canaliculata* matched well with the known distribution, but that of the parasite requires further validation in the field. Although Yunnan province was included in the national sampling survey in 2006 and 2007, no *A. cantonensis* were discovered there (Lv *et al.*, 2009b). However, a previous field survey demonstrated an endemic focus in a setting where Yunnan province borders Vietnam (Li, Zhou & Li, 1989). Hubei province was also reported endemic for *A. cantonensis* in the early 1990s (Zhou *et al.*, 1993), but there were no further reports thereafter. Interestingly, south-eastern Hubei is a region of predicted variable *A. cantonensis* endemicity according to our study. If endemicity of the parasite is confirmed in this area, it is conceivable that the parasite may also be present in the Sichuan basin, where *P. canaliculata* has been well established.

With regard to research needs, it is necessary to confirm the potential transmission pattern of *A. cantonensis* along with the spread of *P. canaliculata* in the face of climate change. In case the *A. cantonensis*–*P. canaliculata* pattern holds, the worm burden of wild rats must be determined in areas where *A. fulica* is absent and terrestrial slugs are scarce. The northern part of Fujian province and southern parts of Zhejiang, Jiangxi and Hunan provinces possibly are suitable for this validation (Lv *et al.*, 2009b).

A second research need is to develop social-ecological models to predict the impact of climate change on infectious diseases. Our biological model emphasised rising temperatures as the main effect of climate change. However, climate change goes far beyond rising temperature. The spread of vectors and intermediate hosts, and hence the transmission of a parasitic disease, is a complex process and other factors (e.g. biodiversity, water velocity and land use patterns, as well as human behaviour and socio-cultural factors) may play equally important roles in the transmission dynamics of vectorborne diseases. There is a need to identify key factors deriving from ecological niche modelling and ecosystem health approaches to address large-scale effects.

In conclusion, we have shown that the interplay of an invasive species in the face of climate change may result in a significant expansion of the current endemic area of an emerging parasitic disease in China. Given the public health importance of angiostrongyliasis, awareness of this disease risk and related research and surveillance must be further strengthened and interventions implemented to halt the spread and establishment of *P. canaliculata*.

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