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Surveillance of clonorchiasis in China in 2016

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ABSTRACT

Clonorchiasis is an important food-borne parasitic disease in China, and infection with *C. sinensis* can cause hepatobiliary diseases. Comprehensive and systematic prevention and control of clonorchiasis requires the establishment of an effective surveillance. A total of 301 surveillance points were set up in 30 provinces across China in 2016, and 1000 people were selected by cluster sampling at each surveillance point annually for *C. sinensis* infection screening using Kato-Katz thick smear method. *C. sinensis* infection was detected in 6226 people following screening of 305081 people at the 301 surveillance points in 2016. Infection rate was 2.04%; with *C. sinensis* infection detected in 70 counties spread across 15 provinces, 89.37% of the infected people were distributed in Jilin, Heilongjiang, Guangdong and Guangxi provinces. Highest infection rate was observed in Da'an city, Jilin Province (49%). The national infection rate in male and female was 2.70% and 1.40% respectively. Infection rate between male and female was significantly different ($P < 0.01$). Disease prevalence increases with age in both male and female, reaches peak in age group 40–49. Result obtained indicate that major *C. sinensis* endemic areas are distributed in the north and south of China, and areas with high prevalence are distributed along the river system at county level. Result, also, shows that middle-aged men are at high-risk of infection. These results suggest that surveillance activities should be sustained nationwide and highlight the need for an integrated approach to control *C. sinensis* transmission in regions with high disease prevalence in China.

1. Introduction

Clonorchiasis is a major food-borne disease in China (Qian et al., 2013), people are infected by eating raw or undercooked freshwater fish that contains metacercaria of *C. sinensis*. Adult worms are parasitic in the human hepatobiliary duct, acute infection can cause varying degrees of gastrointestinal symptoms (Yukio, 2012; Keiser and Utzinger, 2009), and chronic infection can induce cholangiocarcinoma (E.M. Kim et al., 2008; Y.J. Kim et al., 2008; Sripa et al., 2014; Choi et al., 2006). *C. sinensis* infection is classified as "carcinogenic to humans" (Group 1) by the International Agency for Research on Cancer (IARC) in 2009 (Bouvard et al., 2009). Clonorchiasis is predominantly endemic in East Asia, including China, South Korea, Vietnam and Russia Far East. It is estimated that about 15 million people are infected with *C. sinensis* globally, of which China account for 85% of global clonorchiasis distribution (Qian et al., 2012).

Clonorchiasis has been in existence for more than 2000 years in China. *C. sinensis* eggs were found in the intestine of an ancient corpse buried during West Han Dynasty in Jiangling county, Hubei Province in 1975 (Wei et al., 1980). In characteristic manner of *C. sinensis* infection, consumption of raw fish also has a long history of more than 2000 years in the dietary culture of China. The earliest records about eating raw fish can be traced back to the pre-Qin Dynasty, this custom reached its peak in the Tang and Song Dynasties, and became a dietary culture. Description of raw fish consumption was mentioned in numerous poems at that time. The custom of eating raw fish, however, became less attractive nationwide mainly due to loss of expertise in fish production and its' public health implication (Wu, 2017). Currently, sashimi made from freshwater fish remains a local delicacy for entertaining distinguished guests in some areas endemic for clonorchiasis, such as Guangdong (Fang et al., 1994; Pan et al., 2000, 2000), Guangxi (Li et al., 2002; San et al., 1994, 1995) and Heilongjiang province (Kang et al., 1994; Li et al., 2000; Niu et al., 2001). Thus, clonorchiasis remains an important public health problem in these areas.

As indicated in the result of the second national survey of human parasitic diseases in 2004, clonorchiasis is mainly prevalent in Guangdong, Guangxi, Heilongjiang and Jilin provinces in China (Wang, 2008). However, it is pertinent to establish an efficient uninterrupted surveillance system to provide insight on clonorchiasis distribution and also predict disease epidemic trend in China. The Chinese

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Ministry of Health organized and established a surveillance system for clonorchiasis covering 30 provinces in China in 2016, thus, an important step to strengthen prevention and control of clonorchiasis.

2. Materials and methods

2.1. Establishment of surveillance points

The surveillance programme was formulated by the National Institute of Parasitic Diseases (NIPD) of China CDC, received approval from the Chinese Ministry of Health and sent to the provincial CDC. Based on the result of the second national survey of human parasitic diseases in 2004, each provincial CDC chose 5–10 counties as surveillance point every year, and reported the county name to the National Institute of Parasitic Diseases of China CDC. Thereafter, training course for the surveillance plan was carried out step-wisely from the national level to county level. Field investigation was done between September and October yearly, the provincial CDC was saddled with the organization and surveillance quality control responsibilities.

2.2. Sample collections

The county CDCs selected five towns by geographic locations of east, west, north, south and middle, a village was randomly selected from each town, and 200 people were selected from each village by cluster sample. A total of 1000 people were sampled from five villages for stool examination. Collection boxes were sent to the household of selected subjects houses a day prior to collection by the village doctor, who recorded the basic information of the villagers and gave each subject a unique number. Then, the villagers handed over box with fecal samples to the designated place, and the village doctor sent them to the CDC for examination.

2.3. Stool sample examination

Three smears were made by Kato–Katz method for each fecal sample, and was examined for *C. sinensis* eggs by skilled microscopist. The number and species of eggs observed in each smears were recorded.

2.4. Data collection and analysis

The county-level CDC enters the data into the database following examination and report it to the provincial CDC. The provincial CDC examines the database and report it to NIPD through network reporting system, while NIPD is responsible for collation and database analysis as well as compile the annual surveillance report and forward to the Ministry of Health. The calculation of infection rate and chi-square test were completed using SARS (9.2), the chart was made by Excel (2013), and the map was made by ArcGIS (10.1) software.

3. Results

The surveillance of clonorchiasis was carried out in 301 surveillance points distributed in 30 Provinces/Municipalities/Autonomous Regions (P/M/As) in 2016. A total of 305081person was examined of which 6226 individuals were infected with *C. sinensis*, the infection rate was 2.04%. *C. sinensis* infection was found in 70 counties (districts) of 15 P/M/As. The surveillance point with highest infection rate of *C. sinensis* was Da'an City in Jilin Province, and infection rate was 49%. Guangdong, Guangxi, Heilongjiang and Jilin accounted for 89.37% of all *C. sinensis* infections.

3.1. Regional distribution

Surveillance results in 2016 showed that *C. sinensis* infection was found in 15 P/M/As, of which prevalence rates in 5 P/M/As were above 1%, the highest prevalence was 12.69% (Jilin), followed by 10.51% (Heilongjiang), 7.57% (Guangdong), 6.65% (Guangxi) and 3.49% (Hunan). Prevalence rates in the other 10 P/M/As were between 0 and 1%, while no individual was found with *C. sinensis* infection in 15 P/M/As (Table 1). The detailed results are shown in the table below.

Table 1
Prevalence of *C. sinensis* infection in China.

Province	No. of positive	No. of subjects	Infection rates (%)
Jilin	1515	11,940	12.69
Heilongjiang	2031	19,323	10.51
Guangdong	773	10,205	7.57
Guangxi	1245	18,720	6.65
Hunan	495	14,164	3.49
Jiangxi	96	14,178	0.68
Fujian	19	9181	0.21
Jiangsu	5	4150	0.12
Liaoning	14	15,343	0.09
Guizhou	10	12,086	0.08
Shandong	9	14,430	0.06
Sichuan	9	15,482	0.06
Anhui	1	1992	0.05
Xinjiang	3	11,866	0.03
Chongqing	1	6298	0.02
Beijing	0	3005	0.00
Gansu	0	8038	0.00
Hainan	0	2007	0.00
Hebei	0	16,745	0.00
Henan	0	19,422	0.00
Hubei	0	10,229	0.00
Neimenggu	0	9925	0.00
Ningxia	0	4816	0.00
Qinghai	0	8081	0.00
Shanxi	0	5975	0.00
Shaanxi	0	8995	0.00
Shanghai	0	3186	0.00
Tianjin	0	3049	0.00
Yunnan	0	11,052	0.00
Zhejiang	0	11,198	0.00

C. sinensis infection was detected in 70 surveillance sites. The highest infection rate was found in Da'an City, Jilin Province (49.00%), followed by Zhenlai County, Jilin Province (41.3%). There were 31 surveillance sites with infection rates above 1%, 27 of which were distributed in Jilin, Heilongjiang, Guangdong and Guangxi provinces. In addition, high prevalence of clonorchiasis was also found in Tongdao County (23.80%) and Qiyang County (22.38%) in Hunan Province, Xinfeng County (9.25%) in Jiangxi Province and Panshan County (1.38%) in Liaoning Province. The distribution of infection rates at each surveillance county is shown below.

There are two major clonorchiasis endemic regions in China as shown in Fig. 1, these include; Guangdong and Guangxi provinces which are located in southern China, also, Jilin and Heilongjiang provinces in the north. There are 59 surveillance points in the four provinces (Fig. 2), of which, 20 surveillance points are located in Jilin and Heilongjiang provinces along the Songhuajiang River and they accounted for 17.34% (3545/20,446) prevalence rate. Also, 11 of the surveillance points are not adjacent to the Songhuajiang River, and have total infection rate of 0.01% (1/10,817), the difference in infection rate is statistically significant. There are 13 surveillance points in Guangdong and Guangxi provinces along the Zhujiang River with 11.87% (1609/13,554) total infection rate, 15 monitoring points are not adjacent to the Zhujiang River, and have 2.66% (409/15,371) total infection rate (Fig. 3). The difference in infection rate is, also, statistically significant ($P < 0.05$).

3.2. Sex distribution

A total of 150,782 male were investigated in 301 surveillance sites in 2016, of which 4068 were infected and the infection rate was 2.70%

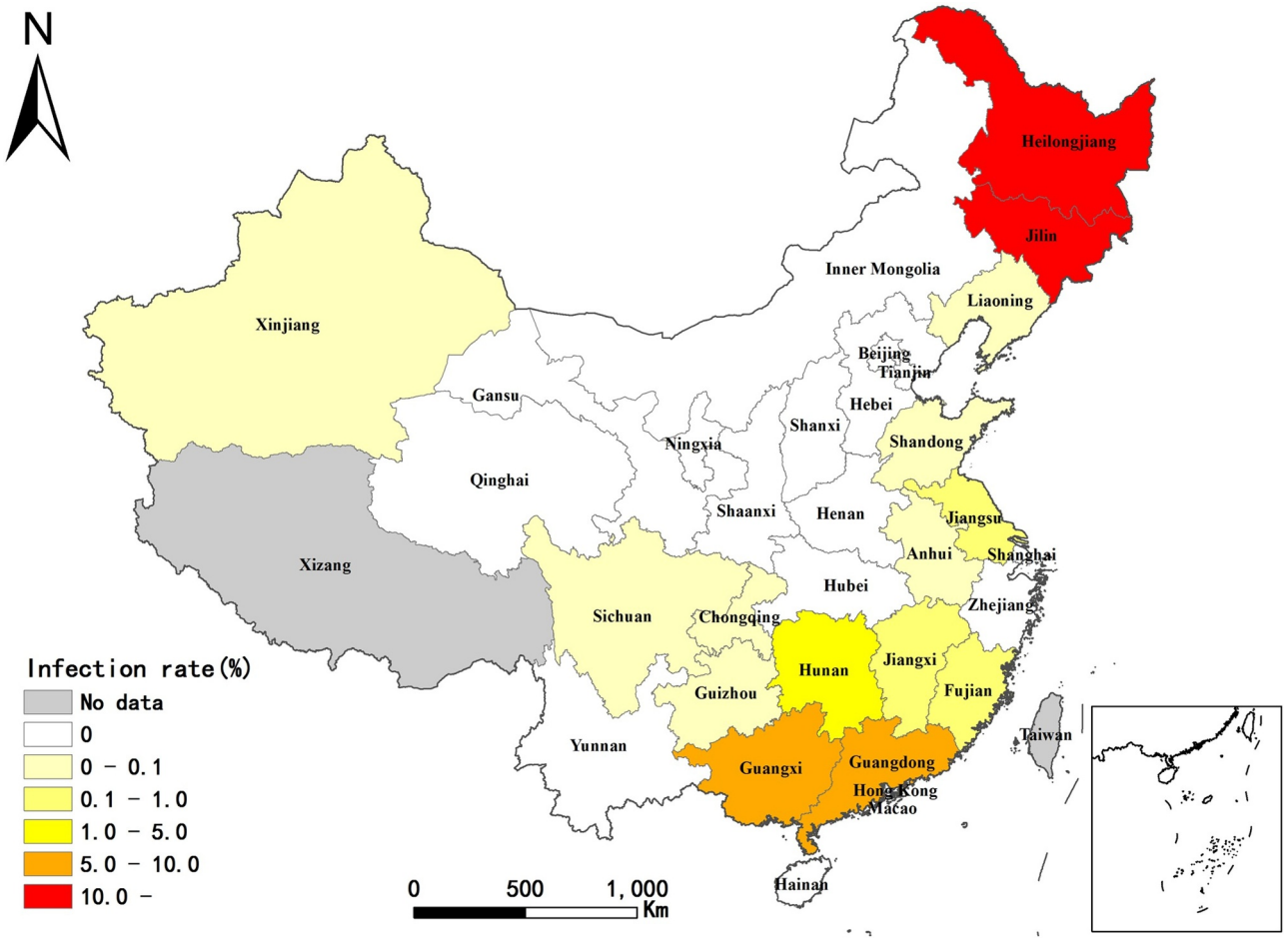

Fig. 1. The distribution of prevalence rate of *C. sinensis* in China 2016.

while 154,491 females were investigated and 2158 were infected, the infection rate was 1.40% (Fig. 4). The difference in infection rate between male and female was statistically significant ($P < 0.05$).

Clonorchiasis prevalence was higher in males than females in the five provinces with prevalence >1%. The difference in infection rate between male and female was statistically significant ($P < 0.01$). Results are shown in Table 2.

3.3. Age distribution

Clonorchiasis prevalence increases with age and highest in age group 40–49 years old, then decreased with age. Infection rates in male and female, also, showed similar trend in age distribution. The male and female infection rates in age group 40 years old was 4.59% and 2.26% respectively (Fig. 5).

Highest clonorchiasis prevalence rate occurred between 40 and 59 age group with 52.3% in the four major endemic regions (Fig. 6). The age distribution of infection rate in key epidemic provinces is shown below:

4. Discussion

Clonorchiasis is mainly caused by active feeding on raw or undercooked fish contaminated with *C. sinensis* parasite. Its distribution is not only related to natural factors, but also closely related to poor human dietary habits and social customs. Our surveillance results show that there are two major clonorchiasis endemic regions in China, which includes; Jilin and Heilongjiang provinces in northeastern region, also, Guangdong and Guangxi provinces in the southern region. This result is consistent with the previous national surveys and research works on *C. sinensis* (Yu et al., 1994; Xu et al., 1995, 2000; Lai et al., 2017). Our findings, also, indicate that clonorchiasis endemic areas both in southern and northern parts of the country are distributed along the river system (Han et al., 2013).Similar distribution pattern was observed in areas endemic with *C. sinensis* in South Korea (Park et al., 2014; June et al., 2013). Most inhabitants in riverine areas are involved in a lot of fishing and aquaculture activities for livelihood. Fish is rich in protein, nutritious and easy to access, thus, an important staple in the diet of the local residents, and also, readily available for promoting the custom of eating raw fish by the locals. Findings indicate that middle-aged men are the most infected population in terms of distribution and proportion. This is similar to results obtained from clonorchiasis surveys carried out in Korea (Park et al., 2014; June et al., 2013), but differs from the prevalence of *Opisthorchis viverrini* a different type of liver fluke which is mainly endemic in some parts of southeast Asian countries, such as Vietnam, Laos, Thailand, Cambodia and Myanmar, where rice mix with raw fish is a very common daily food and there is little difference in the incidence of infection between male and female especially in areas with heavy disease prevalence (Suwannatrai et al., 2018; Sithithaworn et al., 2003; Sayasone et al., 2007; Kobayashi et al., 2000). However, consumption of raw fish is not only a feeding habit, but also a social behavior in China. People usually drink alcohol when eating raw fish believing that the alcoholic content can kill bacteria and parasites in raw fish acting as a disinfectant.

This encourage consumption of raw fish in social occasions such as business dinner, which middle-age men have more opportunities than women and children to participate. This implies that the chances of having infected in adult male population is higher than in children and

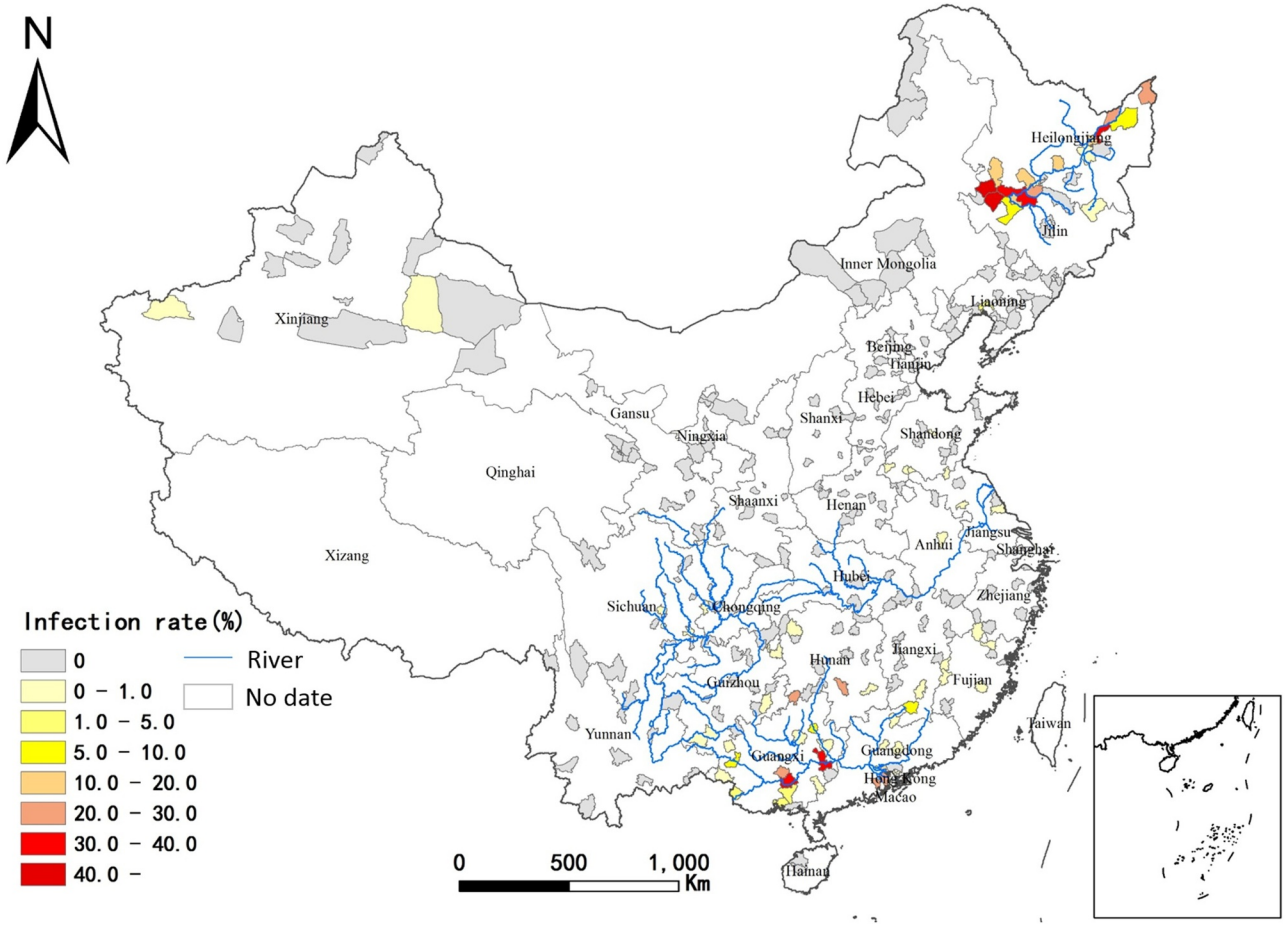

Fig. 2. Distribution of *C. sinensis* infection rates at county level in 2016.

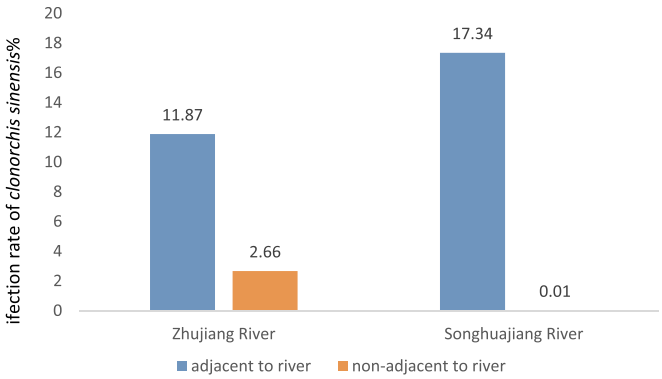

Fig. 3. Comparison of prevalence between counties adjacent to river and those not adjacent to river.

women following the trend in eating behavior. Understanding these differences through monitoring can help provide the basis for developing effective prevention and control strategies.

There are, also, other ways of contacting *C. sinensis* infection in China aside eating raw fish directly. The use of cutting board already used to prepare infected raw fish without thorough washing before use for other food processing purposes such as row and cooked food, grilling small wild-catch fish for snacks and eating fish congee made of dipping row fish in hot rice soup etc. Fish congee is a famous dish in Guangdong province, and is considered good delicacies suitable for infants and young children. This may explain why *C. sinensis* infection rate in children is higher in Guangdong province than the other three provinces. Besides, grilling small wild-catch fish for snacks is another important route for infection in children, especially in rural areas, where older children catch wild fish and grill them as snacks for themselves and their younger siblings. *C. sinensis* infected people in areas with low prevalence, where locals do not inculcate the habit of eating raw fish usually get infected when they taste raw fish out of curiosity whenever they travel to endemic areas or through cross-contamination as a result of using contaminated chopping board.

Clonorchiasis epidemic requires two prerequisites, these include (i). the distribution of intermediate and definitive hosts in the wild allows the parasite to complete its life cycle. *C. sinensis* epidemiology requires two intermediate hosts including the snail hosts and freshwater fish and its distribution is dependent on the intermediate hosts; (ii). The local residents still indulge in the habit of raw fish consumption. It is reported that there are 12 species of freshwater snails that serves as the first intermediate host of *C. sinensis* and 112 species of freshwater fish can act as the second intermediate host in China (Liu et al., 2012). The intermediate hosts have wide distribution in China except the Qinghai–Tibet plateau which implies that clonorchiasis is of public health importance in China (Zhang et al., 2014; Zhao et al., 2005). Studies have shown that *C. sinensis* metacercariae is highly resistant to adverse environmental conditions, which also increases their chances of infecting wild animals (Fan et al., 1998) . Although clonorchiasis prevalence is very low or about zero in some places but disease prevalence can be above 50% in the reservoir host (Tang et al., 2012). The continued habit of eating raw fish or its introduction into areas not endemic for clonorchiasis would trigger *C. sinensis* epidemic in the region. The habit of eating raw fish is regarded as a cultural heritage that should be protected in some endemic areas, they showcase and add glamour to this custom by holding the sashimi cultural festival (Lu, 2009). This eating habit has spread across regions and cities where

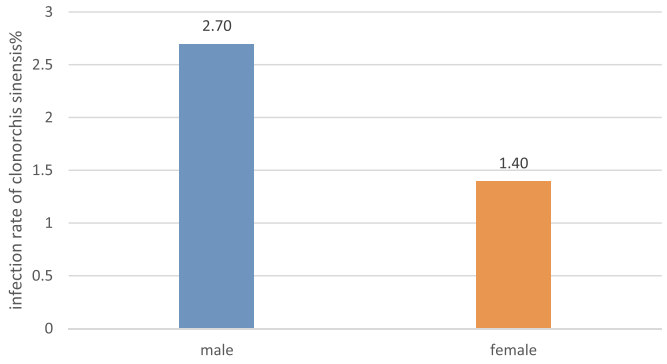

Fig. 4. The sex distribution of *C. sinensis* infection.

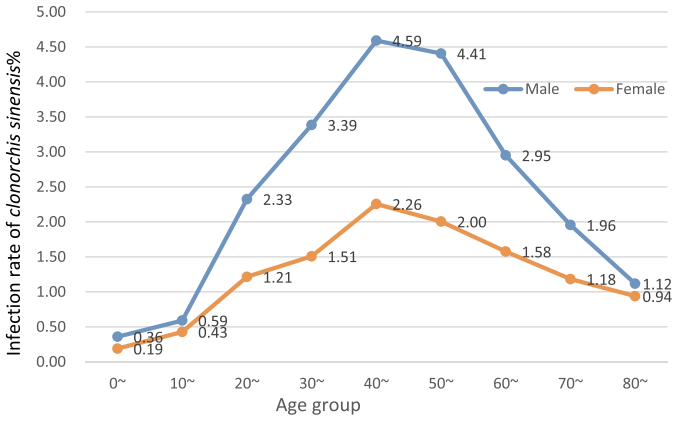

Fig. 5. Age distribution of *C. sinensis* infection.

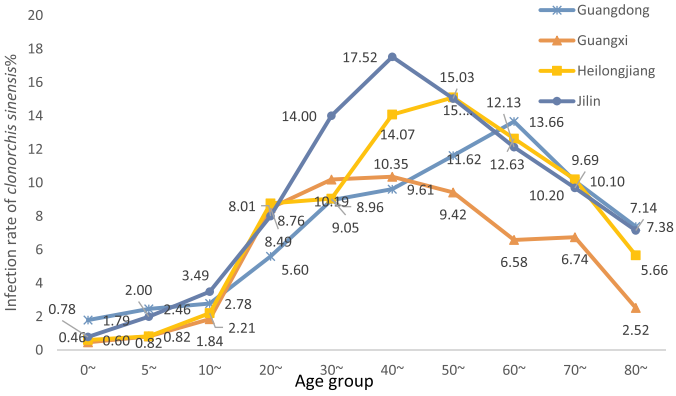

Fig. 6. Age distribution of *C. sinensis* infection in four provinces.

local residents are not known to eat raw fish, sashimi made from freshwater fish are found in restaurants located in these big cities. Such development not only bring obstacles to clonorchiasis prevention and control but also increase the risk of *C. sinensis* transmission in non-endemic region. It is, therefore, necessary to set up monitoring sites in non-endemic areas.

After identifying the epidemic area, it is necessary to select some areas with heavy prevalence for intervention. Comprehensive prevention and control measures have proved to be an effective intervention strategy (Bürli et al., 2018; Tangkawattana et al., 2018), as mentioned above, *C. sinensis* infection is caused by diet-related behaviors or customs, therefore, in addition to mass drug treatment, preventive measures against re-infection can be summarized in two aspects which include; changing people's behavior and reduction or blocking infection in fishes that serve as second intermediate host.

Health education is the main strategy targeting behavioral change in the people (Oh et al., 2014). The content and form of health education are peculiar for different groups, for example, students can be taught about the life cycle and transmission routes in the form of hygiene studies in health education classes, and this would encourage them to share such knowledge with their parents, families and neighbors at home. For young and middle-aged men, multimedia and mobile phone terminals can be used as the platform to educate them about the danger that infection with clonorchiasis poses to their well-being and also advise them to actively go for routine fecal examination and take deworming drugs. While housewives should be given awareness to imbibe good hygiene culture and ensure that their kitchen utensils especially cutting boards and knives are thoroughly washed after usage to avoid cross-contamination. They should also constantly educate their children not to eat undercooked freshwater fish, so as to reduce the risk of infection in preschool children.

Other measures to ensure effective reduction of infection in fish include improve and increase sanitation facilities, improving aquaculture practices (Clausen et al., 2015), strengthen the management of pet cats and dogs (Tangkawattana et al., 2018), and active snail hosts control through reducing snails density in fish ponds. The implementation of these measures requires cooperation of health, fisheries, education and other departments, therefore, effective implementation of comprehensive interventions requires that the local government authorities takes the leading role for efficient coordination. When health authorities recommending local governments to adopt comprehensive control measures the data accumulated by monitor is indispensable.

Although Clonorchiasis has been discovered, recognized and studied for more than 100 years (McConnell, 1875; Hong and Fang, 2012; Qian et al., 2016), the investigation and comprehensive control of clonorchiasis in China started few decades ago. We gradually have a good grasp of clonorchiasis epidemic distribution at the provincial level following the national surveys of human parasitic diseases carried out every 10 years (Yu et al., 1994; Wang, 2008). We have implemented some control measures in clonorchiasis endemic areas and achieved certain level of effectiveness and experiences in the past twenty years with the support of the Chinese Ministry of Health and other international cooperation agencies (Choi et al., 2010; Ji et al., 2012; Huang et al., 2017; Qian, 2014). Although these efforts have achieved significant decline in clonorchiasis prevalence in some high endemic areas through mass drug treatment, but our surveillance data indicate that *C. sinensis* prevalence has risen significantly in those areas following interruption of intervention strategies for several years. This

Table 2
Sex distribution of *C. sinensis* infection in five provinces.

Province	Male			Female			chi-square	*P-value*
	No.of positive	No.of subjects	Infection rate(%)	No.of positive	No.of subjects	Infection rate(%)		
Guangdong	553	5316	10.40	220	4889	4.50	126.74	<0.001
Guangxi	889	9096	9.77	356	9624	3.70	27.93	<0.001
Heilongjiang	1281	10,176	12.59	750	9145	8.20	98.55	<0.001
Hunan	279	6938	4.02	216	7226	2.99	11.18	<0.05
Jilin	965	6115	15.78	550	5824	9.44	108.13	<0.001
Total	3967	37,641	10.54	2092	36,708	5.70	581.61	<0.001

shows that the use of preventive chemotherapy alone is not effective enough to achieve desirable control outcome and also alter the behavior or change the people from eating raw fish because it has been the locals cultural norm for ages. We, therefore, have a long battle to fight against this cultural heritage to effectively control clonorchiasis in all towns and villages where such habit is predominant. Hence, we need to target and focus resources to clonorchiasis hotspots to achieve success with control strategy in China.

It is, therefore, imperative that we implement accurate preventive measures, establish efficient surveillance system and also sustain surveillance activities in order to comprehensively understand the distribution and epidemic situation of clonorchiasis at county level, as well as, predict epidemic trend and formulate precise control strategies.

5. Conclusion

Clonorchiasis is mainly prevalent in four provinces in China namely Guangdong, Guangxi, Heilongjiang and Jilin. The prevalence of *C. sinensis* ranges from 0%−49% and varies significantly across counties. The high prevalence of clonorchiasis is closely related to the distribution of river system at county level. Middle-aged men are at high infection risk in endemic areas. Systematic surveillance was first implemented in 2016, we believe that the accumulation of surveillance data would provide more insight on clonorchiasis epidemic distribution in China.

CRediT authorship contribution statement

Ting-Jun Zhu: Writing - original draft, Writing - review & editing, Investigation, Formal analysis. **Ying-Dan Chen:** Conceptualization, Validation, Writing - review & editing. **Men-Bao Qian:** Methodology, Resources, Writing - review & editing. **Hui-Hui Zhu:** Formal analysis, Data curation, Software, Writing - review & editing. **Ji-Lei Huang:** Visualization, Investigation, Writing - review & editing. **Chang-Hai Zhou:** Supervision, Project administration, Writing - review & editing. **Xiao-Nong Zhou:** Project administration, Funding acquisition, Writing - review & editing.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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