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Spatiotemporal and demographic characteristics of scrub typhus in Southwest China, 2006-2017: an analysis of population-based surveillance data

Running title: Scrub typhus in Southwest China

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Summary

Scrub typhus is a life-threatening vector-borne disease. During the past decade, the number of areas affected by this disease has expanded in many countries. In this study, we aim to identify the spatiotemporal and demographic characteristics of scrub typhus in Southwest China, an emerging endemic region for scrub typhus. Population-based surveillance data capturing scrub typhus cases in two provinces of Southwest China during 2006–2017 were retrieved. Descriptive temporal and spatial analyses were conducted and stratified by age group. The space-time scan statistic was used to identify spatiotemporal clusters of scrub typhus occurrence at the county level. During the study period, 30,001 scrub typhus cases were recorded in Southwest China, with a total of 61.0% (191/313) of counties being affected; most cases (94.3%) occurred in rural areas. The annual incidence rate increased substantially from 0.25/100,000 in 2006 to 5.38/100,000 in 2017 (> 21-fold change). The 0–4-year-old and 45–64-year-old subgroups had the highest cumulative incidence rates (57.46 and 32.98/100,000, respectively). Furthermore, since 2006, the 0–4-year-old (slope=0.83, $p<0.01$) and 45–64-year-old (slope=0.69, $p<0.01$) age groups have had the highest increases in incidence of all age groups. The most likely spatial cluster of overall cases (relative risk=4.13, $p<0.01$) occurred in the southern region of Southwest China and included 41 high-risk counties. In conclusion, scrub typhus appears to be widely distributed and rapidly increasing in Southwest China. Young children and middle-aged adults were the most severely affected groups, and the disease appeared to predominantly cluster in the southern part of Southwest China. Further in-depth surveys to determine the epidemiological characteristics and driving factors of this emerging disease and to facilitate effective control programmes among high-risk groups in the affected areas should be promoted.

Keywords: Demographic, Scrub typhus, Southwest China, Spatiotemporal

Introduction

Scrub typhus is an infectious disease caused by *Orientia tsutsugamshi*, which is transmitted to humans by the bite of trombiculid mites called "chiggers" carrying the bacterium. Scrub typhus is endemic to several countries in the Asia-Pacific region, including China (Derne et al., 2015; Kelly et al., 2009; Sharma et al., 2010), and its incidence has grown dramatically around the world in recent years (Gurung et al., 2013; Lee et al., 2015; Lee et al., 2006; Luce-Fedrow et al., 2018; Paris et al., 2013; Prakash, 2017; Sun et al., 2017; Wu et al., 2016; Xu et al., 2017; Yang et al., 2017). It is estimated that there are currently more than half (55%) of the world's population living in scrub typhus-endemic areas and 1 million cases of scrub typhus annually, but this is likely an under-estimate as its current re-emergence in Asia suggests that this number is likely growing (Paris et al., 2013; Prakash, 2017; Walker, 2016; Xu et al., 2017; Yao et al., 2019), and no licensed vaccines or rapid laboratory diagnosis methods are available to prevent the disease (Yao et al., 2019; Zheng et al., 2019). People are generally infected during agricultural or recreational activities, with the adult farmer population being the most vulnerable to infection. Due to the rapidly changing demographics of rural areas in China, the disease is particularly common among elderly farmers (Wu et al., 2016; Wu et al., 2016).

Scrub typhus remains a serious public health problem in China; new natural foci were continuously reported and confirmed, resulting in a dramatically increased geographical distribution and an about 10-fold increase of the annual case number from 2006 to 2013 (Yao et al., 2019). Temporal and demographic heterogeneity of the disease was preliminarily observed between northern and southern regions (Yao et al., 2019). This has highlighted the need to understand the various epidemiological characteristic of the disease existed at different region. Cases mostly occur in the mid-east, southwest and southeast of China. Approximately 25% of reported scrub typhus cases are from Southwest China (Yunnan and Sichuan provinces) (Wu et al., 2016; Wu et al., 2016). In this study, we describe the spatiotemporal and demographic characteristics of scrub typhus in Southwest China using data from the national reporting system for 2006 to 2017. The aim of this study is to identify high-risk areas and populations to help local health departments formulate public health strategies, initiate early preventive measures and conduct enhanced surveillance, thereby reducing the risk of scrub typhus epidemics.

Materials and methods

Study area

Southwest China, which includes Yunnan and Sichuan provinces, covers approximately 880,000 km^2, with approximately 40.9 million hectares of forest cover (Fig. 1) and a warm, humid climate. The population reached approximately 131 million people in 2017. The two provinces are divided into 313 counties with a mean county population density of 487 people/km^2 (ranging from 4 to 12,329 people/km^2). The mean forested area per county is ~1,226 km^2 (range: 0–8,833 km^2), the mean elevation is ~1,586 metres (range: 298–4,502 metres), the mean annual average temperature is ~15°C (range: -11°C to 23°C), the mean annual average sunshine hours is ~1,442 hours (range: 748–2,428 hours), the mean annual average precipitation is ~1,034 mm (range: 413–1,669 mm), and the mean gross domestic product (GDP) is ~0.42 million Chinese Yuan (CNY) (range: 0.02–5.9 million) (Statistics Bureau of Sichuan Province, 2017; Statistics Bureau of Yunnan Province, 2018).

Data collection

In this study, we obtained data on scrub typhus cases in Yunnan and Sichuan from 1 January 2006 to 31 December 2017 from the Chinese Center for Disease Control and Prevention (China CDC). Individual case information (including demographic information, residential code illness onset and diagnosis date, diagnosis type and reporting institution) for each scrub typhus patient was reported by clinicians in the hospitals to the web-based National Notifiable Infectious Disease Reporting Information System (NNIDRIS) of the China CDC. All cases of scrub typhus were diagnosed according to unified diagnostic criteria issued by the Chinese Ministry of Health, which include definitions of suspected, probable and confirmed cases (Chinese Center for Disease

Control and Prevention, 2009). All data used in this study were anonymized so that individual patients could not be identified.

A suspected case was defined as follows: (1) an individual who experienced possible outdoor exposure to mite bites three weeks before the onset of illness, i.e., during farming, fishing, camping, or straw collection, during the epidemic season of the disease (from May to November south of the Yangtze River and from October to November north of the Yangtze River); who presented with fever, lymphadenopathy and skin rash; and for whom diagnoses with other common diseases such as typhus fever, dengue fever or haemorrhagic fever with renal syndrome had been excluded; or (2) an individual whose exposure history to mite bites was uncertain but who developed fever, lymphadenopathy and skin rash during the local epidemic season of scrub typhus. A probable case was defined as follows: (1) a patient with a suspected case with the specific eschars/ulcers of scrub typhus; or (2) an individual who participated in an outdoor activity three weeks before illness onset and presented with fever and the specific eschars/ulcers of scrub typhus. A confirmed case was defined as follows: (1) a suspected or probable case with any of the following three laboratory test results: A) a four-fold or greater increase in serum IgG antibody titre (diluted from 1:32 in two-fold increments) for mixed antigenic slides (including Karp, Kato, Gilliam and Kawasaki) between acute and convalescent sera detected by using an indirect immunofluorescence antibody (IFA) assay (Hu et al., 2015), B) detection of the *O. tsutsugamushi* 56-kDa gene by polymerase chain reaction (PCR) in clinical specimens, or C) the isolation of *O. tsutsugamushi* from clinical specimens (Chinese Center for Disease Control and Prevention, 2009).

Population census data for every county in Southwest China from 2006 to 2017 were retrieved from the National Bureau of Statistics of China.

Data analysis

All probable and confirmed cases were enrolled in the analysis. We estimated the cumulative incidence rate, ratio of males to females, number of rural and urban cases, number of deaths, and case fatality ratio (number of deaths divided by number of cases) stratified by age group (0–4, 5–14, 15–44, 45–64 and ≥65 years old). The cumulative incidence for the overall and specific age groups was calculated by dividing the cumulative number of scrub typhus cases by the corresponding population and multiplying the value by 100,000. To analyse the time series of scrub typhus cases in Southwest China, we created a scatter plot with smooth lines using an autoregressive model of the annual incidence of cases reported in each year from 2006 to 2017 for each age group, and the slopes were calculated for each line using joinpoint regression models (Kim et al., 2000; Yang et al., 2017). A combined histogram was produced to examine the seasonality and its trend of incidence of scrub typhus for overall and different province.

Firstly, to examine global spatial clustering dependency, we used Global Moran's *I* (GeoDa 1.14.0, Luc Anselin) to define spatial autocorrelation in overall scrub typhus cases at the county level, in which a negative value indicates a dispersed distribution and a positive value indicates a clustered distribution. Then, the space-time scan statistic was calculated for each age group to test whether the cases were distributed randomly over space and time and, if not, to locate space-time clusters and determine their statistical significance (an inference that cannot be made from the simple visualization of the raw data). A discrete Poisson model was applied to estimate the relative risk (RR) of each cluster and the log likelihood ratio (LLR) to identify primary and secondary clusters. The significance of clusters was evaluated using 999 Monte Carlo replications. In our study, for each case, the spatial unit was the county of the residence, the individual data was aggregated into unit of county by using the residential code for each case (each case had an eight digits code, cases with the same first six digits of the code were in the same county), and the temporal unit was the month of the onset of illness. In the SaTScan software, a default maximum spatial cluster size of 50% of the whole population was used. A maximum spatial cluster size of 10% of the whole population was also employed to detect possible smaller sized clusters. The maximum temporal cluster size was set at 50% of the study period (Kulldorff, 1997; Kulldorff & Nagarwalla, 1995; Li et al., 2012). As many statistically significant clusters can be identified in each model, we show only three clusters (the primary, or most likely cluster, and the two secondary clusters with the highest LLRs) for each model in the figure and table.

The geographical information system software ArcGIS 10.2.2 (ESRI, Redlands, CA, USA) was used to visualize the scrub typhus clusters; SaTScan version 9.4.4 was employed to implement the space-time scan statistic (Kulldorff, 1997; Kulldorff & Nagarwalla, 1995; Li et al., 2012); and the R statistical software (version 3.4.1, R Foundation for Statistical Computing) with the package *ggplot2* was used to create time series graphs.

Results

Descriptive analysis

During 2006–2017, 30,001 scrub typhus cases were reported in Southwest China, of which 26,898 (89.7%) cases were from Yunnan Province and 29121 (97.1%) were probable cases, 880 (2.9%) were confirmed cases. The cumulative incidence was 23.7 cases/100,000. A total of 28,279 cases (94.3%) occurred in rural areas, and 191 counties (61.0%) were affected by scrub typhus. Thirteen deaths were identified, for a case fatality ratio of 0.043% (Table 1).

From 2006–2017, the median age of patients was 38 years with a range from 0 to 96 years. The 0–4- and 45–64-year-old age groups had the highest cumulative incidence (57.46 cases/100,000 and 32.98 cases/100,000, respectively) (Table 1), and the same age distribution was found both in Yunnan and Sichuan provinces (Table 1). During 2006–2017, the annual incidence rate increased sharply, from 0.25/100,000 in 2006 to 5.38/100,000 in 2017 (>21-fold increase, slope=0.43, p<0.01), and this increasing trend was apparent in all age groups (Fig. 2) but higher among the 0–4-year-old (slope=0.83, p<0.01) and 45–64-year-old groups (slope=0.69, p<0.01) (Fig. 2).

Seasonal variation was apparent in both Yunnan and Sichuan provinces, with the number of cases increasing rapidly starting in May, peaking in August and then decreasing through September; 93.6% of cases occurred between June and November (Fig. 3).

The number of affected counties increased from 109 in 2006–2009 to 151 in 2010–2013 and 173 in 2014–2017, with most being located in Yunnan Province. The counties with a cumulative incidence >50/100,000 were mainly located in the western and southern regions of Yunnan and the border areas of Sichuan and Yunnan (Fig. 4).

Spatiotemporal cluster analysis

The scrub typhus cases were clustered in Southwest China and the spatial correlation was strong (Moran's $I = 0.46$, $p<0.01$). Fig. 5, Additional file 1 and Additional file 2 show the results of the spatiotemporal cluster analysis from spatial scan statistics, stratified by all cases and selected age groups. Using a maximum spatial cluster size of $\leq 50\%$ of the total population, one statistically significant cluster was identified for all cases and then for each specific age group. The cluster for all cases covered 41 counties (radius= 293.84 km) with a duration from July 2014 to November 2017 and an overall RR of 4.13 ($p<0.01$); the clusters for the focal 0–4 and 45–64 age groups covered between 24 and 48 counties in the southern region of Southwest China, respectively.

Using a maximum spatial cluster size of $\leq 10\%$ of the total population, the location of the most likely clusters for all cases and the selected age groups were similar to those found in the analysis using a maximum spatial cluster size of $\leq 50\%$ of the total population. Ten clusters (including the most likely cluster and the secondary clusters) were identified for all the cases. The most likely cluster covered 5 counties and had a duration from July 2013 to November 2017 (RR=4.29, $p<0.01$). Most of these counties were in Dehong Prefecture located along the frontier between China and Myanmar. Furthermore, we identified between 9 and 12 clusters for the specific age groups, with the most likely cluster and two secondary clusters (No. 1 and No. 2) being dispersed throughout Yunnan Province and the southern region of Sichuan Province ($p<0.01$) (Fig. 5, Additional file 1 and Additional file 2).

Discussion

In this paper, by analysing a surveillance dataset spanning 12 years, we demonstrated that the incidence of scrub typhus had increased rapidly in Southwest China, with young children (0–4 years) and middle-aged adults (45–64 years) being the two most affected groups. Cases were primarily clustered in the southern region of Southwest China for all age groups.

In China, natural and socioeconomic factors may have caused the increased risk of scrub typhus infection. Recently, the recovery of forests and wetlands, the banning of the traditional burning of straw within rural areas, and the reduction in industrial land use have produced a suitable setting for the growth of the rodent and mite populations, increasing the possibility of human exposure and the formation of new natural foci for scrub typhus in previously unaffected areas (Liu et al., 2008). In some other endemic countries, there is also evidence suggesting that a combination of climate change and the expansion of humans into previously uninhabited areas may play a role in the rising incidence of scrub typhus (Li et al., 2014a; Tsai & Yeh, 2013). Moreover, during the past two decades (Zhang et al., 2013), rapid change in the demographic structure had been identified in rural areas in China. Many young adults have gone to cities to seek job opportunities with higher incomes, and in many cases, their parents and young children remain in rural areas. Subsequently, in these rural areas, middle-aged people now perform most of the agriculture activities, which can increase the risk of scrub typhus infection among this age group (Wu, Qian, Magalhaes, et al., 2016; Zhang et al., 2013). This might explain the high incidence and increased rate of scrub typhus among 45–64-year-olds. Interestingly, the incidence rate among children aged less than five years was the highest among all age groups. This result differed from those in other areas in China, where 0–4-year-olds had the highest incidence among people aged under 20 years but a much lower incidence than those aged over 45 years (Wu et al., 2016; Wu et al., 2016; Zhang et al., 2013). One hypothesis for the different pattern of age distribution is that farmers in Southwest China might be more likely than farmers in other regions to take their children with them during field activities, creating more opportunities for the children to be infected with scrub typhus (Sun et al., 2017).

The distribution of hosts and vectors in Southwest China may be the reason why scrub typhus cases were most likely clustered in the southern region of Yunnan Province. Previous studies have shown that the species of chigger mites able to transmit scrub typhus in China include *Leptotrombidium deliense*, *L. scutellare*, *L. rubellum*, *L. kaohuense*, *L. insulare* and *L. jishoum* (Peng et al., 2017; Wu et al., 2013). *L. deliense* and *L. scutellare* are the major vectors of scrub typhus in China. *L. deliense*, in particular, is an important transmission vector for scrub typhus in many countries, including India, Burma, Thailand, Australia and the Philippines (Geng, 2013; Lv et al., 2018), and furthermore, *L. deliense* is the major mite species and main vector south of the Yangtze River in China, in provinces such as Guangdong, Fujian, Yunnan and Sichuan. The primary hosts of the mite are *Rattus losea*, *R. norvegicus* and *R. tanezumi*. Mite populations appear in April, peak during June and August, and decrease in September, a temporal distribution similar to that for scrub typhus south of the Yangtze River in China (Wu et al., 2013). *L. rubellum* is also an important transmission vector that is distributed primarily along coastal areas from Changle to Xiamen in Fujian Province in eastern China and in the low-latitude areas of Yunnan Province. This vector mainly appears in July and August, and the primary hosts are *R. losea* (Fujian Province) and *R. tanezumi* (Yunnan Province). A study of the vectors and hosts of scrub typhus in Yunnan Province found that 79.5% of *L. deliense* and 99.1% of *L. rubellum* were distributed in the low-latitude areas (near the Tropic of Cancer), such as Jinghong, Ruili and Puer in the southern regions of Yunnan (Geng, 2013). The distribution of vectors and hosts likely explains the clustering of scrub typhus in areas of Southwest China. The environmental and meteorological factors may play an important role on the distribution of the vector and host in the Southwest China. The endemic foci of the disease are usually in areas of secondary vegetation wherein scrub and grasses appear to provide a suitable habitat for the trombiculid mite vector and rodent hosts and serve as a platform for the parasitic larval stage to attach to passing ground-dwelling vertebrate hosts. Densely vegetated areas close to domestic dwellings are suspected as the sites of scrub typhus transmission (Zheng et al., 2019). Besides, previous studies showed that temperature, relative humidity and precipitation were positively associated with scrub typhus incidences, which may be due to the responses of chiggers to the environmental changes (Li et al., 2014b). According to the approximately 1 km×1km gridded NVDI (Normalized Difference Vegetation

Index) and precipitation dataset, and data from local statistical bureau, the south part of Yunnan developed a higher value of NDVI and precipitation (annual cumulative precipitation) compare to other areas of Southwest China, which may be the driving factors of high incidence of scrub typhus.

Our study has two limitations. Firstly, All the data used were collected from a passive disease surveillance system, and scrub typhus is not a notifiable communicable disease in China. Therefore, under-reporting is likely an issue. With a passive reporting system, the under-reporting of surveillance data is inevitable and will certainly affect the precision in measuring the absolute number of cases and the incidence rates. However, data used in this study were the most comprehensive and reliable data on scrub typhus available at national and subnational levels in China. Besides, as the aims of this study were to compare the relative trend, age distribution and geographic pattern, it is reasonable to assume that the situation of under-reporting was similar across the different years, age groups and regions; therefore, it should be less likely that the results in our study are impacted by under-reporting. Secondly, most cases (97.1%) in our study were probable cases and weren't under confirmatory laboratory test, which meant most cases were diagnosed by the presence of eschar. However, other diseases, such as spotted fever group of rickettsioses, insect bites (including spider bites), posttraumatic scabs and anthrax can include an inoculation eschar at the surface of the skin (Xin et al., 2019). All these diseases associated with an eschar could increase the chance of misdiagnosis and influence the accuracy of our results. But according to the case definition, a patient was diagnosed as probable case based on their epidemiology history and clinical symptoms like fever, lymphadenectasis and skin rash. Besides, clinically, a medical worker usually diagnosis a patient as scrub typhus according to the apparent effect of the lipid solubility antibiotics (such as azithromycin). All of these conditions can be distinguished with other diseases above. Besides, the proportion of probable and confirmed cases remain stable during our study period (Additional file 3). Therefore, for overall, the resulted obtained in our study could reflect the true distribution of this disease in the Southwest China.

Overall, our study demonstrated that scrub typhus has been spreading widely and increasing rapidly in Southwest China and that children and middle-aged people were the most affected population groups. The disease seemed to be mainly clustered in southern regions of Southwest China. These findings highlight that scrub typhus has become a potential great public health threat to high-risk groups in the affected areas. Further in-depth surveys should be conducted to comprehensively define the epidemiological features of this disease. In Southwest China, immediate measures should be taken in high-risk areas to increase health education and awareness of scrub typhus, enhance treatment and diagnostic practices, and continually improve surveillance of this emerging infectious disease.

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Ethics statement

Not applicable.

Data accessibility statement

All data generated or analysed during this study are included in this published article and its additional files.

Conflict of interest

The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of scrub typhus cases by age group in Southwest China, 2006–2017

	Overall	0–4	5–14	15–44	45–64	≥ 65
No. of cases (n, %†)	30,001 (100)	4,134 (13.8)	3,684 (12.3)	10,208 (34.0)	9,667 (32.2)	2,308 (7.7)
No. of probable cases (n, % ‡)	29,121 (97.1)	4,009 (97.0)	3,514 (95.4)	9,894 (96.9)	9,460 (97.9)	2,244 (97.2)
No. of confirmed cases (n, % ‡)	880 (2.9)	125 (3.0)	170 (4.6)	314 (3.1)	207 (2.1)	64 (2.8)
Yunnan (n, % ‡)	26,898 (89.7)	3,786 (91.5)	3,245 (88.1)	9,151 (89.6)	8,697 (90.0)	2,019 (87.5)
Rural (n, %§)	25,229 (93.8)	3,500 (92.4)	3,047 (93.9)	8,686 (94.9)	8,154 (93.8)	1,842 (91.2)
Urban (n, %§)	1,669 (6.2)	286 (7.6)	198 (6.1)	465 (5.1)	543 (6.2)	177 (8.8)
Sichuan (n, % ‡)	3,103 (10.3)	348 (8.5)	439 (11.9)	1,057 (10.4)	970 (10.0)	289 (12.5)
Rural (n, %§)	3,050 (98.3)	339 (97.4)	428 (97.5)	1,038 (98.2)	961 (99.1)	284 (98.3)
Urban (n, %§)	53 (1.7)	9 (2.6)	11 (2.5)	19 (1.8)	9 (0.9)	5 (1.7)
Annual average population (million)	126	7.19	16	61.6	29.3	12.3
Overall cumulative incidence (per 100,000)	23.74	57.46	23.06	16.57	32.98	18.75
Yunnan	58.52	129.75	49.10	38.56	94.48	57.60
Sichuan	3.86	8.14	4.69	2.79	4.82	3.28
Sex-ratio of males to females	0.97	1.30	1.44	0.97	0.77	0.80
No. of counties with cases	191	121	128	166	164	120
Deaths	13	5	0	2	4	2
Case fatality rate (‰)	0.43	1.21	0	0.20	0.41	0.87

†: percentage of all cases; **‡:** percentage of cases in each age group; **§:** percentage of cases in each age group by province.

Figure legends

Fig. 1 The geographic location of Sichuan and Yunnan provinces of Southwest China, 2006–2017 (GADM, 2019).

Fig. 2 Temporal trend of scrub typhus incidence in Southwest China, 2006-2017 by age group

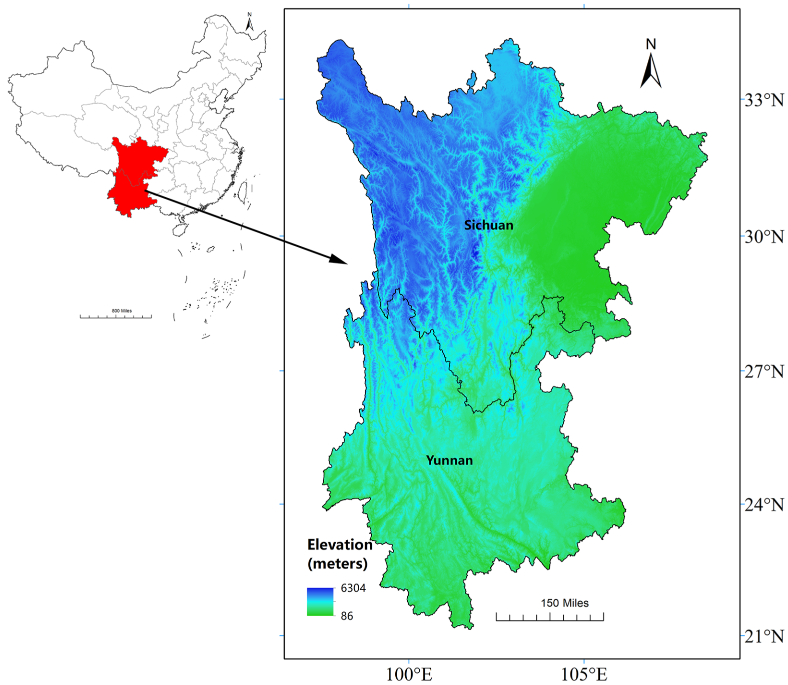
Fig. 3 The seasonal distribution of scrub typhus cases in Southwest China. A) Overall; B) Yunnan; C) Sichuan.

Fig. 4 The geographic distribution of the cumulative incidence rate in Southwest China (GADM, 2019). A) During 2006 to 2009; B) During 2010 to 2013; C) During 2014 to 2017.

Fig. 5 The spatial clusters of scrub typhus for the total cases and for the 0–4-year-old and 45–64-year-old age groups in Southwest China, 2006-2017 (GADM, 2019). A, B, C) Clusters of scrub typhus cases for the total cases and for the 0–4-year-old and 45–64-year-old age groups with a maximum spatial cluster size ≤50% of the total population; D, E, F) Clusters of scrub typhus cases for the total cases and for the 0–4-year-old and 45–64-year-old age groups with a maximum spatial cluster size ≤10% of the total population.

Additional file 2 The spatial clusters of scrub typhus for the total cases and for the 0–4-year-old and 45–64-year-old age groups in Southwest China, 2006-2017. A, B, C) Clusters of scrub typhus cases for the total cases and for the 0–4-year-old and 45–64-year-old age groups with a maximum spatial cluster size ≤50% of the total population; D, E, F) Clusters of scrub typhus cases for the total cases and for the 0–4-year-old and 45–64-year-old age groups with a maximum spatial cluster size ≤10% of the total population.

Additional file 3 Proportion of probable and confirmed cases reported by year.



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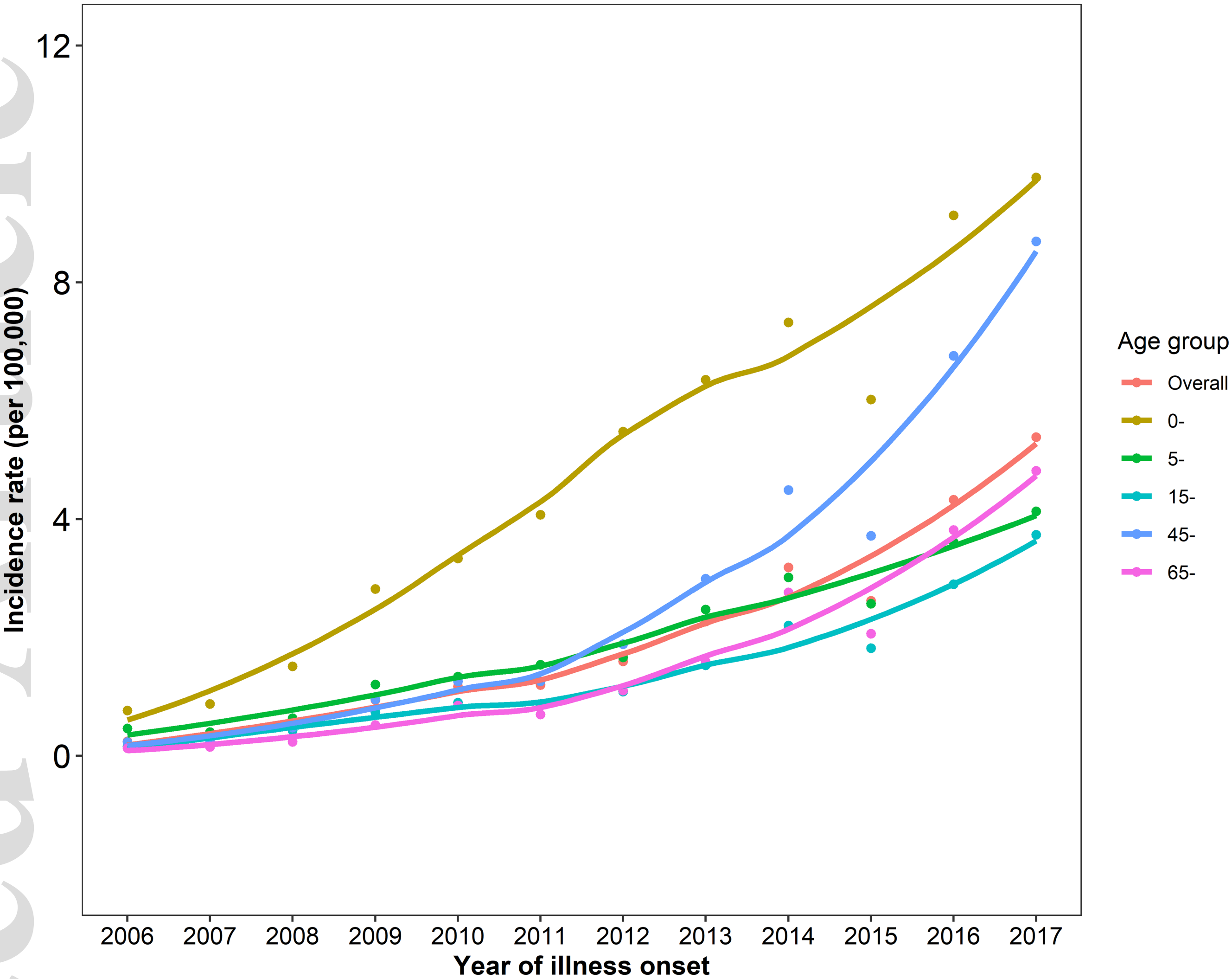

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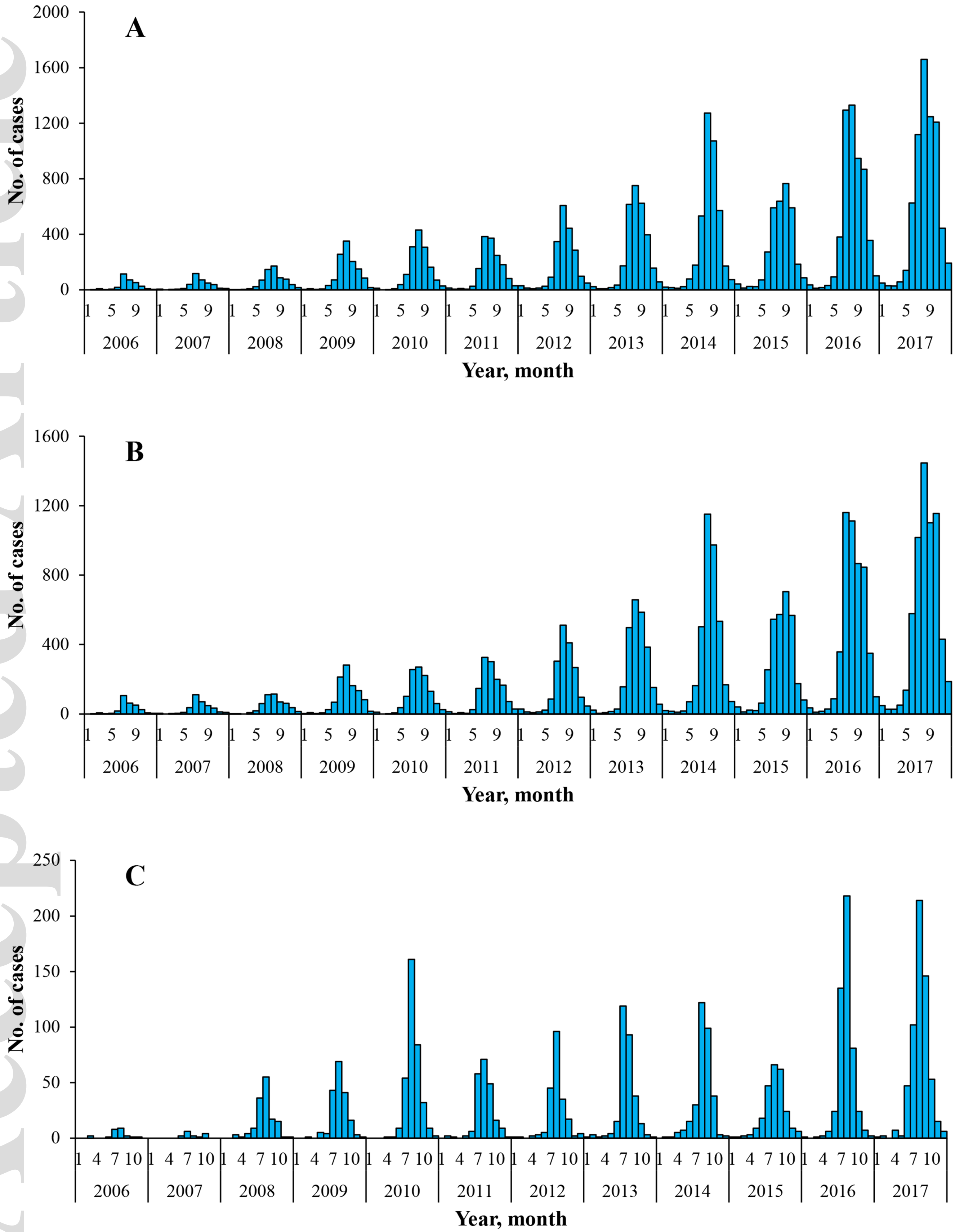

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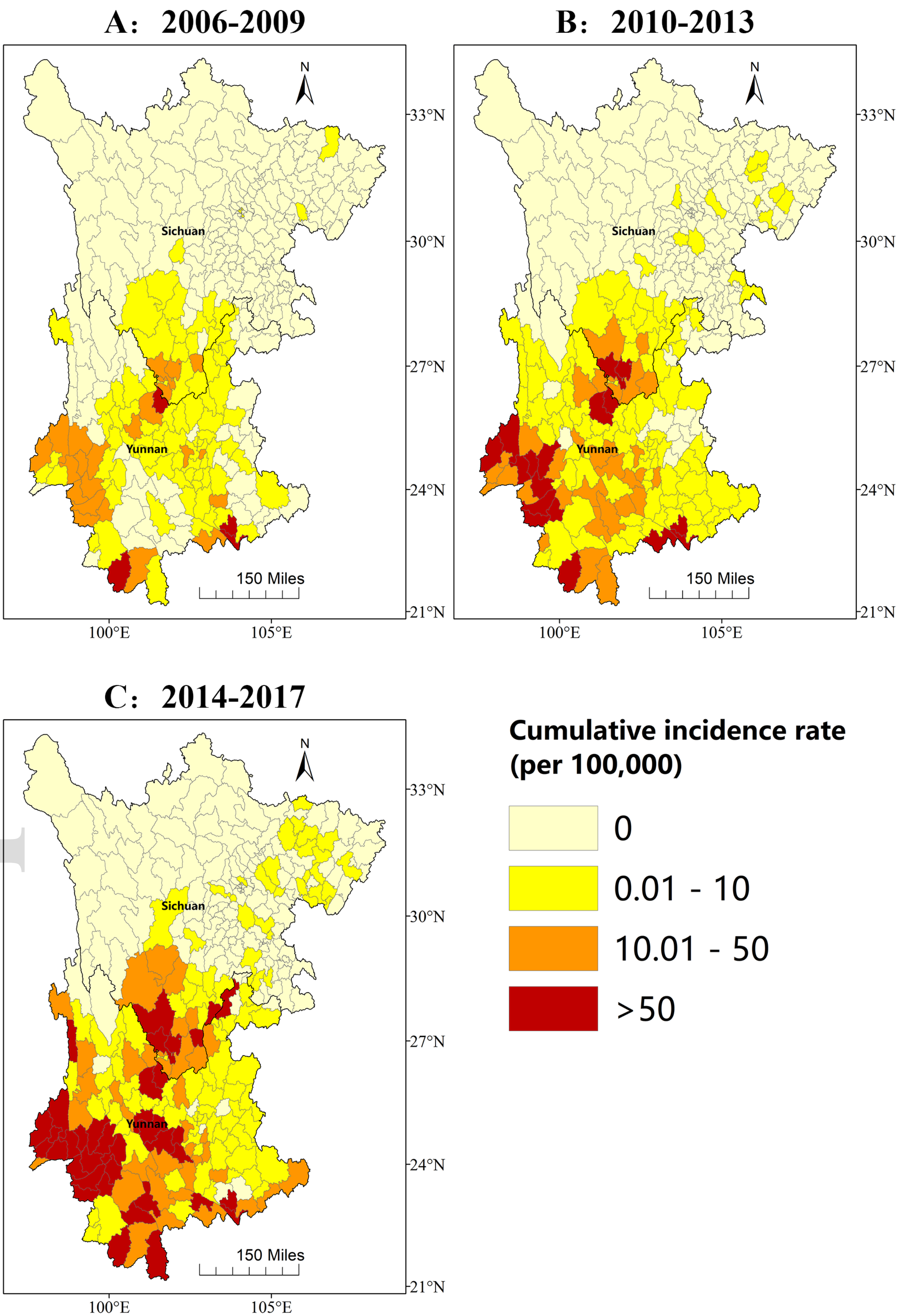
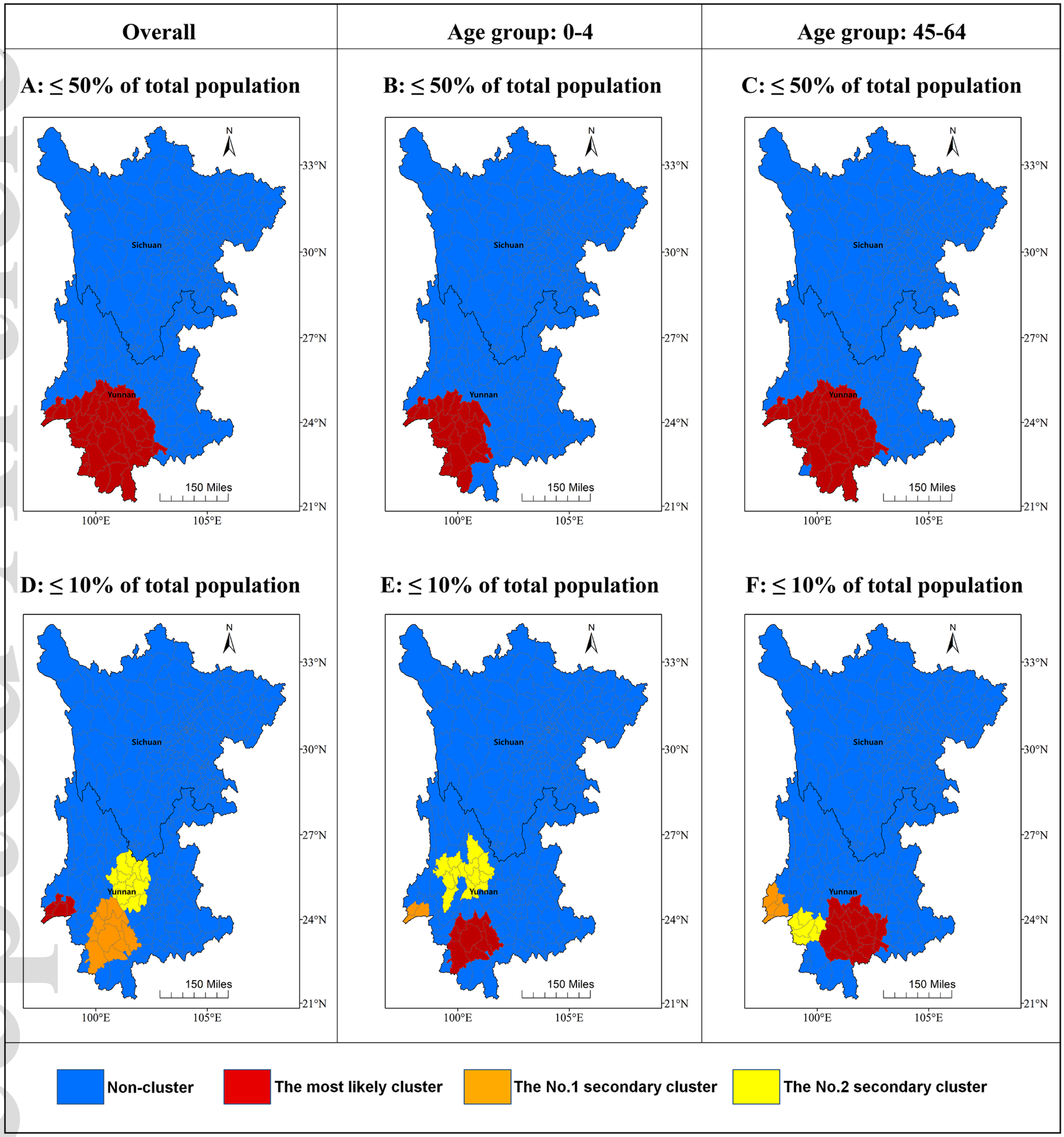

A：2006-2009
B：2010-2013
C：2014-2017
Sichuan
Yunnan
N
150 Miles
33°N
30°N
27°N
24°N
21°N
100°E
105°E
Cumulative incidence rate
(per 100,000)
0
0.01 - 10
10.01 - 50
>50



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