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Rapid Increase in Scrub Typhus Incidence in Mainland China, 2006–2014

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Abstract. Scrub typhus is a vector-borne disease, which has recently reemerged in China. In this study, we describe the distribution and incidence of scrub typhus cases in China from 2006 to 2014 and quantify differences in scrub typhus cases with respect to sex, age, and occupation. The results of our study indicate that the annual incidence of scrub typhus has increased during the study period. The number of cases peaked in 2014, which was 12.8 times greater than the number of cases reported in 2006. Most (77.97%) of the cases were reported in five provinces (Guangdong, Yunnan, Anhui, Fujian, and Shandong). Our study also demonstrates that the incidence rate of scrub typhus was significantly higher in females compared to males ($P < 0.001$) and was highest in the 60–69 year age group, and that farmers had a higher incidence rate than nonfarmers ($P < 0.001$). Different seasonal trends were identified in the number of reported cases between the northern and southern provinces of China. These findings not only demonstrate that China has experienced a large increase in scrub typhus incidence, but also document an expansion in the geographic distribution throughout the country.

INTRODUCTION

Scrub typhus, also called tsutsugamushi disease, is a vector-borne infectious disease primarily endemic in several Asia–Pacific nations.[1,2] Scrub typhus is an infection caused by the intracellular pathogen *Orientia tsutsugamushi*, which can be transmitted to humans after being bitten by trombiculid mites or "chiggers" carrying the bacterium.[3,4] The clinical manifestations of scrub typhus can range from unapparent or atypical febrile illness to life-threatening symptoms including acute hearing loss and multiple organ failure.[5,6] It is estimated that there are currently more than 1 billion people living in scrub typhus endemic areas, and the incidence has begun to increase over the last decade.[7] Though largely sensitive to doxycycline, rifampicin, and azithromycin, *O. tsutsugamushi* is inherently resistant to treatment with β-lactam antibiotics and aminoglycosides, and an effective vaccine is currently not available.[8]

Scrub typhus remains a serious public health problem in China. The first case of human infection with *O. tsutsugamushi* in China was identified in 1948 in Guangzhou, Guangdong Province. The number of reported cases increased over the following decades until reaching a peak incidence in the 1980s. Disease outbreak or case report registration of scrub typhus has been cancelled since 1990; however, according to related researches, the intensity of the disease has strengthened. Therefore, as a result of the recent reemergence of cases throughout the country over the last decade, scrub typhus has become a component of China's National Notifiable Disease Surveillance System.[9]

Historically, scrub typhus mainly occurred in southern provinces of the Yangtze River before the 1980s, which included Zhejiang to the east and Yunnan to the west. Recently, case reports and new natural foci of scrub typhus have been identified in the northern provinces of Shandong, Jiangsu, and Tianjin.[9,10] Although the incidence and geographic distribution of reported cases has increased, scrub typhus remains a neglected tropical disease in China. Furthermore, despite the relatively low mortality, scrub typhus has the potential to cause a significant burden on public health, resulting in economic losses, and create serious challenges for both travel- and military-related operations.[11] Previous studies in China have investigated the epidemiological features of scrub typhus in some provinces or cities, but the nationwide trends in reported cases have yet to be adequately characterized.[10,12]

In this study, we describe and quantify the epidemiological characteristics of scrub typhus to provide a better understanding of the distribution and incidence of this emerging infectious disease in China. The results from the study will provide a foundation of evidence for national, provincial, and local health-care authorities to design strategies to mitigate the health effects of scrub typhus throughout China.

MATERIALS AND METHODS

Ethics statement. This study was approved by the ethics committee of Beijing Institute of Disease Control and Prevention, and all data were de-identified for the purpose of maintaining confidentiality before analysis.

Data collection. Scrub typhus is a nationally notifiable disease in China that physicians must report to the China Center for Disease Control and Prevention through the China Information System for Disease Control and Prevention (CISDCP). The case definition for scrub typhus consists of an individual who has traveled to an endemic area or reported contact with chiggers or rodents 1–3 weeks before the onset of illness, presented with clinical manifestations such as high fever along with characteristic skin rash and eschars/ulcers, and at least one of the following laboratory

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criteria: agglutination titer ≥ 1:160 in the Weil–Felix test using the OX-K strain of *Proteus mirabilis*, a 4-fold or more rise of antibody titer against *O. tsutsugamushi* using the indirect immunofluorescence antibody assay, detection of *O. tsutsugamushi* by polymerase chain reaction in clinical specimens, or isolation of *O. tsutsugamushi* from clinical specimens.[13] Individual case data from 2006 to 2014 were obtained from CISDCP, which included demographic information such as sex, age, and occupation along with the residential address, date of symptom onset, clinical diagnosis, and clinical outcome for each case.

Statistical analysis. For the purpose of analysis, seasonal variation in the disease incidence was investigated by aggregating cases into monthly intervals and age differences were investigated by stratification of the cases into age groups of 10-year intervals. The geographic distribution of scrub typhus was examined using counties as the unit of analysis and also divided into two regional datasets (one north and one south of the Yangtze River) to quantify differences in the temporal distribution of scrub typhus cases between regions. The differences in the incidence rates of scrub typhus cases by sex, age group, and occupation were analyzed using the χ^2 test. The temporal trend was investigated by Cochran–Armitage trend test. All statistical analyses were performed with SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Descriptive analyses. A total of 54,558 scrub typhus cases, including 37 deaths, were reported during the study period, of which 25,640 were male patients (47%) and 28,918 were female patients (53%). The difference in scrub typhus incidence was significantly higher in females compared with males ($\chi^2 = 399.22$, $P < 0.001$). Although the sex-specific incidence was not significantly different from 2006 to 2010 ($P > 0.05$), between 2011 and 2014 females had a higher incidence than males ($P < 0.001$). The number of cases increased annually for each age group during the study period (Table 1). The greatest number of cases occurred in the age group of 50–59 years, which accounted for 22% of the total reported cases. Similarly, the higher incidence rate was observed in the older age groups where the age groups of 50–59, 60–69, and ≥ 70 years had the three highest annual incidence of 0.79/100,000, 1.15/100,000, and 1.07/100,000, respectively (Table 1). By occupation, farmers had a higher incidence of scrub typhus than those who did not classify their occupation as farming, with the proportion of cases identified in farmers increasing from 58.65% in 2006 to 73.85% in 2014 ($z = 151.64$, $P < 0.001$). The time between symptom onset to clinical diagnosis of scrub typhus ranged from 1 to 39 days and had a median of 7 days, with most patients (88.55%) diagnosed within 2 weeks of symptom onset. In addition, 37 deaths associated with scrub typhus were reported, which comprised 21 males and 16 females. The majority (94.60%) of deaths occurred in southern provinces, especially in Guangdong (54.05%), Fujian (13.51%), Guangxi (10.81%), and Yunnan (10.81%).

Spatial and temporal distributions. The annual incidence of scrub typhus increased significantly during the study period ($z = 172.14$, $P < 0.001$). Our study results demonstrate that the number of scrub typhus cases regularly peaked in July and October each year (Figure 1A). The number of cases reached a peak in 2014, where the number of reported scrub typhus cases was 12.8 times higher than the number of cases reported in 2006 (Table 2). Though 1,031 counties from 29 provinces in mainland China reported scrub typhus cases during the study period, the majority of cases (77.97%) were reported from only five provinces (Guangdong, Yunnan, Anhui, Fujian, and Shandong). Among the top 10 provinces with reported cases of scrub typhus, seven provinces were located south of the Yangtze River, and compared with the north (23.45%), comprised the majority of all reported cases with 72.90% (Figure 2, Table 2). In 2014, a total of 768 counties reported scrub typhus cases, which was 3.6 times larger than the number of counties that reported cases in 2006 (Table 2). The number of counties with reported cases demonstrated an increasing trend over 9-year period that was highly significant ($z = 28.05$, $P < 0.001$).

Seasonal differences between northern and southern provinces. Our analysis identified differences in the seasonal trends in incidence between northern and southern provinces (Figure 1). In Fujian, Guangdong, and Guangxi, the scrub typhus cases initially increased in May and was followed by a large peak in June or July before a slight decline, and then

TABLE 1
Epidemiologic features of scrub typhus cases in mainland China, 2006–2014

	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total	Incidence rate* (1/100,000)
Sex											
Males	639	708	1,379	1,658	2,036	2,871	4,207	4,912	7,230	25,640	0.42
Females	609	628	1,228	1,575	2,047	3,127	4,679	6,205	8,820	28,918	0.50
Age group											
< 10	178	168	297	478	562	646	914	1,036	1,265	5,544	0.38
10–19	88	93	137	226	226	274	354	400	569	2,367	0.14
20–29	72	91	202	234	279	404	467	614	877	3,240	0.17
30–39	149	178	283	396	490	551	816	989	1,395	5,247	0.28
40–49	198	196	469	593	738	1,086	1,666	2,066	2,824	9,836	0.51
50–59	279	289	565	645	833	1,275	1,964	2,473	3,679	12,002	0.79
60–69	179	191	379	384	609	1,035	1,605	2,162	3,270	9,814	1.15
≥ 70	105	130	275	277	346	727	1,100	1,377	2,171	6,508	1.07
Farmers											
Yes	732	858	1,699	2,077	2,719	4,239	6,150	7,857	11,852	38,183	0.49
No	516	478	908	1,156	1,364	1,759	2,736	3,260	4,198	16,375	0.41
Total	1,248	1,336	2,607	3,233	4,083	5,998	8,886	11,117	16,050	54,558	

*Annual average incidence.

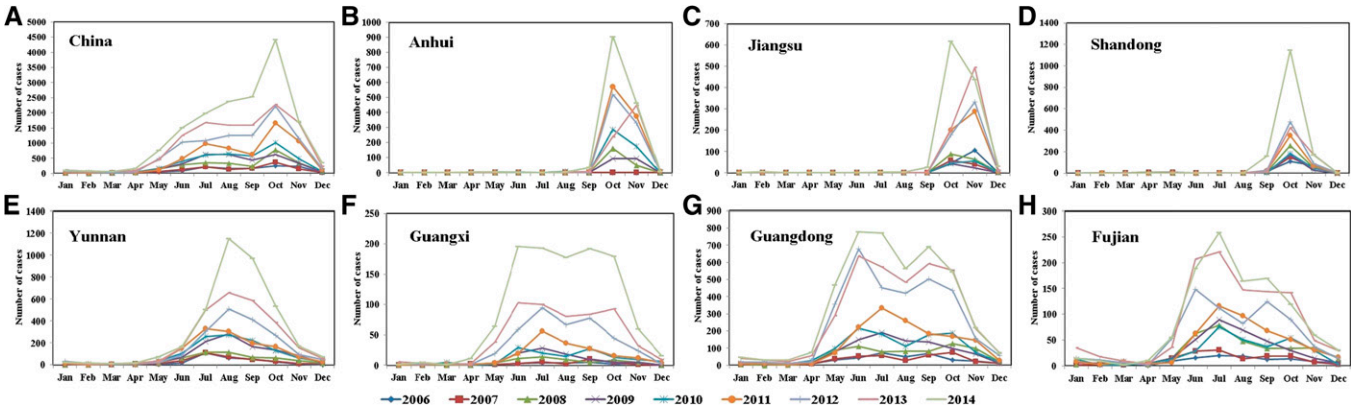

FIGURE 1. Temporal distribution of scrub typhus cases in China, 2006–2014. (**A**) Nationwide and in seven provinces: (**B**) Anhui, (**C**) Jiangsu, (**D**) Shandong, (**E**) Yunnan, (**F**) Guangxi, (**G**) Guangdong, and (**H**) Fujian with most reported cases were analyzed to observe seasonal variation between north and south regions.

revealed a small peak in September or October with a continuous decrease thereafter; in Yunnan, the number of cases demonstrated a single large peak in July or August. In contrast, the northern provinces (Shandong, Anhui, and Jiangsu) demonstrated a later seasonal onset of reported scrub typhus cases between September and December, with a single large peak in October or November every year.

DISCUSSION

The results of this study demonstrate that between 2006 and 2014 there has been an alarming increase in the number of reported cases of scrub typhus in China, indicating that scrub typhus remains an important public health problem throughout the country. Given the trends identified in this study, our findings suggest that scrub typhus incidence will likely continue to increase in the future. Furthermore, the results of our study also identified seasonal differences in the onset and duration of scrub typhus that suggest the existence of both summer and autumn transmission of scrub typhus in China. During the period of 2006–2014, the temporal distribution of reported scrub typhus cases followed a bimodal seasonal pattern characterized by two yearly peaks observed between July and October, which is similar to that observed in Japan but different from that of Korea.[4,14] This seasonal trend was previous thought to be attributed to the abundance of different species of chiggers or rodents as well as more outdoor activities in warmer seasons.[15] Our study extends current knowledge with regard to the seasonal pattern of scrub typhus in China in that the summer peak seems to be linked to geographical differences between the northern and southern provinces.

Our study also confirmed that farmers and those aged 60–69 years old were the groups most at risk due to increased exposure to infected mites and poor protection during agriculture or field recreational activities. The results showed that in recent years the incidence among females was higher than that observed in males, which can be partly explained by increased proportion of females engaging in outdoor activities or occupations.[16] Notably, the results also demonstrated a nonlinear risk of scrub typhus by age group, where children aged less than 10 years had a higher incidence rate than the older age groups (i.e., 10–20 and 20–30 year old age groups). This could be the result of lower awareness of scrub typhus and reduced use of protective measures when playing in grassland or woods.[11]

The results of our study indicated that from 2006 to 2014 scrub typhus occurred mainly in southern provinces and also documented an increase in both the number of reported cases and counties that reported scrub typhus cases. The increase of scrub typhus in southern provinces could be associated with societal changes. In the past decades, the prosperity of ecotourism resulted from the development of western regions in provinces such as Guangxi, Yunnan, and Sichuan as well as the large increase of floating population in Guangdong and Zhejiang. This change in the population distribution could have increased the rate of human exposure to forests, riverbanks, and grassy regions that provide optimal environmental conditions for infected mites to thrive.[11,15] Moreover, the results showed deaths caused by scrub typhus mainly occurred in southern provinces, which could be explained by differences in the virulence of *O. tsutsugamushi* strains or by differences

TABLE 2
Annual cases and counties with scrub typhus cases, top 10 provinces with scrub typhus cases, mainland China, 2006–2014

	No. of cases (%)	No. of counties (%)	Incidence* (1/100,000)
Year			
2006	1,248 (2.29)	216	0.10
2007	1,336 (2.45)	221	0.10
2008	2,607 (4.78)	322	0.20
2009	3,233 (5.93)	367	0.25
2010	4,083 (7.48)	426	0.31
2011	5,998 (10.99)	500	0.46
2012	8,886 (16.29)	574	0.68
2013	11,117 (20.38)	691	0.85
2014	16,050 (29.42)	769	1.22
Southern province			
Guangdong	15,978 (29.29)	128 (12.43)	1.85
Yunnan	12,673 (23.25)	121 (11.75)	3.08
Fujian	4,535 (8.31)	89 (8.64)	1.37
Guangxi	2,547 (4.67)	102 (9.90)	0.58
Sichuan	1,752 (3.21)	49 (4.76)	0.24
Jiangxi	1,489 (2.73)	46 (4.47)	0.37
Hainan	789 (1.45)	22 (2.14)	1.02
Northern province			
Anhui	4,878 (8.94)	77 (7.48)	0.88
Shandong	4,463 (8.18)	87 (8.45)	0.52
Jiangsu	3,453 (6.33)	73 (7.09)	0.50

*Annual average incidence.

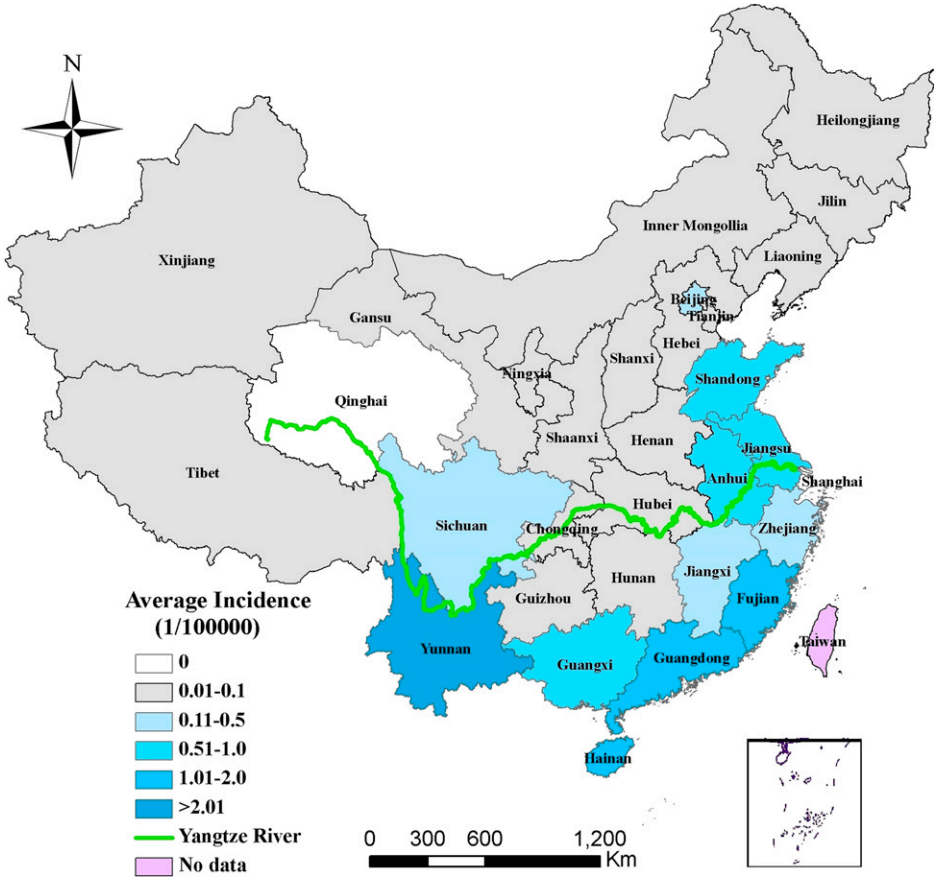

FIGURE 2. Geographic distribution of scrub typhus incidence in mainland China, 2006–2014.

in vector competence between regions. In southern provinces of China, the primary vector of scrub typhus, *Leptotrombidium deliense*, is associated with higher pathogenicity compared with *Leptotrombidium scutellare*, which is the dominant species in the northern provinces.[15,17]

This study also documented the expansion of new natural foci in the northern provinces with the identification of the first outbreak of scrub typhus in Anhui Province in 2008.[18] Since then, the number of cases in Anhui demonstrated a rapid increase with similar expansions occurring elsewhere in Beijing, Shaanxi, and Henan.[9,19] Previous studies suggested that the translocation of infected rodents or chiggers from adjacent regions may have led to the formation of new foci of infection in those provinces.[20]

In conclusion, our study demonstrates that scrub typhus incidence in China has recently undergone a significant increase and expansion of its geographical distribution throughout mainland China. It is possible that environmental and socioeconomic factors could be important drivers in both the establishment of new natural foci and the continued transmission of the disease; the role of these determinants warrant further exploration. Since these data were obtained from a passive surveillance system, it is entirely possible that some cases of scrub typhus were not identified, and active surveillance could help to clarify trends in scrub typhus transmission. If the trends identified by this study continue, our findings suggest the incidence of scrub typhus could rapidly increase in the near future. Given the magnitude of these findings, people living in southern regions of China, especially elderly people and those working in agricultural settings, should be made aware of the symptoms and risk factors associated with scrub typhus. Targeted measures aimed at these high-risk populations should also be investigated to mitigate the effects of this emerging infectious disease.

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