ORIGINAL ARTICLE

# Factors associated with Scrub Typhus infection: A case-control study from Luhe, China

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**ABSTRACT**

**Introduction:Scrub typhus (ST) is an acute febrile infection and remains a significant health problem globally. This study aimed to determine the factors associated with ST infection in Luhe District, China.**

**Material and Methods: The case-control study was conducted among 116 cases identified through passive surveillance systems over three years.The control subjects were 232 living in the same village for more than six months without any history of ST infection were selected by matching to the age (within 5-years) and identified through active surveillance. Statistical analyses were performed using SPSS v. 25.0 for Windows (IBM SPSS, Chicago, IL, USA).**

**Results: The mean age of confirmed persons was 58.1(SD=10.15) years, while control subjects were 56.14 (11.57).There is no significant difference in gender, age, education, and occupations between case and control. Farmers had the most significant number of cases among occupational groups. The three factors that were significantly associated with an increased odds of having ST infection are bundling or moving waste straw (OR: 1.94, 95%CI; 0.99,381), morning exercise in the park or field (OR: 4.74 95%CI; 1.19, 18.95), and working as labourer in the vegetable field (OR:1.02, 95%CI:1.02,3.19).**

**Conclusions:Our findings suggested establishing a prevention and control strategy for these groups to lower ST development risk.**

**KEYWORDS:**
*Scrub typhus, Orientia tsutsugamushi, Case-control study*

## INTRODUCTION

Scrub typhus (ST) is an acute febrile infectious disease caused by *Orientia tsutsugamushi*. Globally, ST remains a significant health problem, affecting millions of people every year, and evidence has shown that more than one billion people are at risk due to the non-availability of effective vaccines or vector control efforts.[1] The most prevalent transmission mode of *Orientia tsutsugamushi* to humans is through the bites of infected larval mites known as "chiggers" (belonging to the family Trombiculide).[2] Both rodents and mites are reported as the natural reservoir and hosts of the virus.[3] The incidence of ST mortality rates ranged from <1% to 50% depending upon proper antibiotic treatment, the status of a person infected, and the strain of *Orientia tsutsugamushi* encountered.[4]

The endemicity potency of ST has occurred within a 13,000,000 km$^2$ area of Asia, mainly in the Asia Pacific tsutsugamushi triangle, and remained a burden over a considerable long period of time.[5] These endemic areas extend from northern Japan to the East and North of Russia. It connects to the north of Australia in the South and Pakistan and Afghanistan in the West and the Western Pacific islands and East Asia, including China.[1] In China, ST remains one of the most severe public health concerns. Historically, southern China was known as ST endemic region, and subsequently, the disease expanded to other provinces in both rural and urban areas.[6]

The incidence of ST in China increased 1952-1989 and 2006-2016, where 133,623 cases and 174 deaths were reported.[6] There was tremendous widespread and re-emergence of ST cases identified in the past decade in many regions, including Qingdao city, China.[7] It was recently documented in high-incidence areas in the mainland of China,[8,9] with an emerging and increasing threat for many people in Guangdong province, China,[10] Zhejiang Province,[11] Anhui Province,[12] north China, Shandong province,[13,14] and recently in Jiangsu Province, China.[15] In 2006, ST was added to the national infectious disease surveillance system as a voluntarily reportable disease mainly prevalent in tropical and subtropical regions.[7,10,13] A published case-control study documented that the developing risk factors of ST occur through agricultural exposure, such as working in rice fields in Thailand, Japan, and South Korea. This also occurred among those working in oil palm and rubber plantations in Malaysia.[16]

Previous epidemiological studies have identified that those people engaged in fruit farming, gathering chestnuts, who took breaks in the areas adjacent to Korea's agriculture operations are at risk of ST infection,[17] and also the people living in rural areas. In particular, the risk is more among people age 40 and above, and people with nonfarming occupations are reported to be at higher risk of death in China.[6] Other factors associated with the increase inST infection are through outdoor activities, particularly in rural areas and among the people living at the village edge of Jiangsu Province, and bundling or moving waste straw.[18]

*This article was accepted: 19 May 2021*
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Also, the rapid urbanization of the populations and modifications in the ecological environment contribute to the increase of ST incidence.[19] In settings susceptible to ST, the risks are higher for people living close to grassland and cemented floor yards.[20] Furthermore,those engaged in agricultural activities like piling weeds working in hilly areas and fields are at increase risk of ST infection.[20] Similarly, there is substantial evidence that those working in a dry field farming and livestock industry are increasingly exposed to ST in South Korea.[21] Other community-based case-control studies established that the distribution, re-emergence, and associated factors of ST infection are due to increased outdoor activity of urban people, rapid urbanization, aging populations, and public surveillance systems.[22]

A recently study reported an increase of ST in China.[23] Many studies concerning ST in China have only focused on the serological diagnosis and treatment of ST patients. However, some studies of ST-associated factors have been done in the other ST endemic regions,[18,20,22] Little attention has been given to assess the risk factors in other areas. Thus, we conducted a case-control study to identify the factors associated with ST infection in Luhe District, Nanjing, that might provide information and evidence-based prevention and control.

## MATERIALS AND METHODS

This study was a case-control study conducted in Luhe district (Fig I), with a population of more than 67.74 million (2019) in the Northern part of Nanjing an area of 1485.50 km$^2$. This region has been considered as the main endemic area of ST. The native population here are mainly employed in industries and agricultural sectors.

We used a case-control design and 116 cases (101 of patients were diagnosed positively by serological method, and 15 cases were diagnosed positively by polymerase chain reaction (PCR) were considered. To obtain cases, we sought ST records from a passive surveillance system of data retrospectively gathered from medical record obtained from the Nanjing network of the surveillance system of Nanjing Municipal Center for Disease Prevention and Control, Jiangsu province, China, during the seasonal outbreak spanning from October 2015 to December 2017. Conversely, active surveillance was involved through prospective steps in identifying ST cases, and trained interviewers visited patients in the study area and identified matched control who may develop ST infections.

A total of 232 controls matched with cases were recruited to participate in the study (1：2 pair matching). Eligible controls were defined as active cases living in the same village for more than six months and were matched for age (within five years) and lacked ST history. If matched control was not available in the nearest household, the health staff chose the next household.In addition, several ST associated factors were considered in the following areas: Demographic characteristics of respondents; living environment of ST cases and controls; and places of agricultural labor, outdoor agriculture activities, and human behaviors factors in ST cases and controls.

Ethical approval was obtained from the Institutional Review Board (IRB) of the ethics committee of Jiangsu Province and Nanjing Municipal Center for Disease Prevention and Control in charge of the Ethics Committee of Research School of Public Health. All aspects of the study comply with the Declaration of Helsinki. A verbal and written informed consent were also obtained from all research subjects before conducting the survey.

After consent eligible individuals, a face-to-face interview was used to collect data using a standardized questionnaire validated by the Chinese Center for Disease Control and Prevention based on the Guidelines of ST in China. The questionnaire comprised three main sections: socioeconomic demographic factors, living habits, and outdoor activities previously presented by Lyu et al., 2013.[24] This questionnaire was developed in Chinese. Two trained research enumerators were engaged from the district CDC of Nanjing administrative territory and were trained on the research intent, procedures, and data collection technicality. The data collection was by the staff from the Centre for Disease Control and Prevention (CDC) who were highly knowledgeable in disease surveillance.

Data were entered using Epidata 3.1 (Jens M. Lauritsen, Odense, Denmark), and analysis was done using SPSS version 25.0 for Windows (IBM SPSS, Chicago, IL, USA). Continuous data were expressed as the mean (SD). Descriptive data were presented as frequency and percentage (n (%)) for categorical data, while Chi-square or Fisher's exact test (when appropriate) was used for categorical data to find a potential association between study variables.The goodness-of-fit of the model was evaluated using Hosmer_lemeshow $\chi 2$ statistics. All variables with a p-value of < 0.25 were considered for possible inclusion in a multivariate conditional logistic regression model.The adjusted Odd Ratios and the confidence interval set 95% CI were reported to predict the dimension of factors associated with ST. An alpha value of 0.05 was considered statistically significant.

## RESULTS

Among all the 116 cases and 232 controls, 55 (47.4%) were males, and 61(52.6%) were females. The mean age was 58.1(10.15) years in cases and 56.14 (11.57) in control groups. The age group, 41-60, had the predominant number of cases proportion at 61 (52.6%) in the case and 118 (50.9%) in the control group. Occupation-wise, 90 (77.6%) cases and 187 (80.6%) controls were farmers. Out of the total, 73 (62.9 %) of cases and 145 (62.5%) of control were in primary school (Table I).

The living environment of the case and controls are summarized in (Table II). The findings showed that most of the cases and control groups 67 (57.8%) and 170 (73.3%), respectively, were living at the center of the village and town, and 96 (82.8%) and 142 (61.2%) were living in houses near grassland vegetable field or ditch (P=0.001), 44 (37.9%) and 14 (6.0) piling weed in the yard, and 66 (56.9%) and 196 (45.7%) lived in a house environment where the presence of mouse activities were observed. Thus, residential location, living in houses near grassland, vegetable field or ditch,

**Table I: Demographic characteristics of respondents (N = 116 case, and 232 controls)**

| Characteristics | Characteristics | | p-value* |
|---|---|---|---|
| | Case (n=116) | Controls (n=232) | |
| Gender | | | 0.762 |
| Males | 55 (47.4) | 114 (49.1) | |
| Females | 61 (52.6) | 118 (50.9) | |
| Age Mean (SD) | 58.1(10.15) | 56.14 (11.57) | 0.123 |
| Age group, year | | | 0.359 |
| 20~40 | 5 (4.3) | 19 (8.2) | |
| 41~60 | 61 (52.6) | 123 (53.0) | |
| >61 | 50 (43.1) | 90 (38.8) | |
| Education level, years | | | 0.517 |
| ≤ 6 years | 73 (62.9 | 145 (62.5) | |
| > 6 years | 43 (37.1 | 87 (37.5) | |
| Occupations | | | 0.510 |
| Farmer-related | 90 (77.6) | 187 (80.6) | |
| Non-farming activities | 26 (22.4) | 45 (19.4) | |

*Computed using Chi-square or Fisher's exact test

**Table II: Living environment of ST cases and controls**

| Characteristics | Characteristics | | p-value* | Odds Ratio | 95% CI |
|---|---|---|---|---|---|
| | Case (n=116) | Controls (n=232) | | | |
| Residential location | | | 0.005 | | |
| Edge of village | 49 (42.2) | 62 (26.7) | | 0.513 | 0.29,0.88 |
| Center of village and town | 67 (57.8) | 170 (73.3) | | | |
| House type | | | 0.519 | | |
| Independent house | 83 (71.6) | 174 (75.0) | | 1.069 | 0.59,1.93 |
| Apartment /other | 33 (28.5) | 58 (25.0) | | | |
| House yard with cement floor | | | 0.826 | | |
| Yes | 29 (12.5) | 203 (87.5) | | 0.73 | 0.31,1.72 |
| No | 13 (11.2) | 103 (88.7) | | | |
| Living in houses near grassland, vegetable field or ditch | | | 0.001 | | |
| Yes | 96 (82.8) | 142 (61.2) | | 0.35 | 0.19,0.66 |
| No | 20 (17.2) | 90 (38.8) | | | |
| Piling weeds in the yard | | | 0.001 | | |
| Yes | 44 (37.9) | 14 (6.0) | | 0.12 | 0.06,0.24 |
| No | 72 (62.1) | 218 (94.0) | | | |
| House environment presence of mouse activities | | | 0.054 | | |
| Yes | 66 (56.9) | 196 (45.7) | | 0.89 | 0.53,1.49 |
| No | 50 (43.1) | 126 (54.3) | | | |

*Computed using Chi-square or Fisher's exact test; Abbreviations: (Odds Ratio&95%CI, Confidence Interval) are computed using binary logistic regression.

piling weeds in the yard environments, and house environment the presence of mouse activities are significant factors associated with ST infection.

The potential exposure of place of work and outdoor activities where exposure within one month is presented in (Table III). From the data, there is a significant relationship between the case and controls working as labor in the vegetable field (p=0.003), and those raising animals (dogs, pigs, goats, sheep, and rabbits) (p=0.001), bundling waste straw (P=0.008), having morning exercise in the parks or fields (p=0.001) and fishing (p=0.017), respectively.

*The multivariate analysis output found that three factors are significantly associated with ST infection.*

The three factors that were significantly associated with an increased odds of having ST are bundling or moving waste straw (OR: 1.94, 95% CI; 0.99,3.81), morning exercise in the parks or fields(OR: 4.74, 95% CI; 1.19,18.95), and working as laborers in vegetable fields (OR: 1.80, 95% CI; 1.02,3.19).Good calibration was also observed in the validation set, with $\chi^2$= 6.645 a non-significant P-value of 0.575 derived from the Hosmer-Lemeshow test between the observed and expected events (Table IV).

## DISCUSSION

Scrub typhus is known to be an endemic disease in the world with an exponential increase in spread,[25] including China.[10,23,26-28] Over the years, there has been an increase in the reported case from many parts of China like Beijing,20 Tai'an, Northern China,[29] Jiangsu,[15] and southern China,and rapidly spreading provinces across rural and urban areas.6 This study confirms the potential risk of ST that has been articulated in the previous finding of a recent survey conducted in Jiangsu.[15] Also, the same risk factors of ST identified in Beijing,[15] Korea,[20] Taiwan,[25] Guangzhou,[30] Qingdao city, China.[7]

In the present study,we found that the population of Luhe District is more likely to be infected with ST infection with the

**Table III:Places of agricultural labor, outdoor agriculture activities, and human behaviours factors in ST cases and controls**

| Exposure within one month | Characteristics | | p-value* | Odds Ratio | 95% CI |
|---|---|---|---|---|---|
| | Case (n=116) | Controls (n=232) | | | |
| Places of agricultural labor | | | 0.510 | | |
| Farming –related | 90 (77.6) | 187 (80.6) | | 0.99 | 0.54,1.82 |
| Non-farming | 26 (22.4) | 45 (19.4) | | | |
| Working as labour in rice field | | | 0.551 | | |
| Yes | 18 (15.5) | 43 (18.5) | | 0.94 | 044,2.03 |
| No | 98 (84.5) | 189 (81.5) | | | |
| Working as labour in sweet potatoes fields | | | 0.872 | | |
| Yes | 16 (13.79) | 35 (15.09) | | 0.64 | 0.25,1.68 |
| No | 100 (86.21) | 197 (84.91) | | | |
| Working as labour in vegetable field | | | 0.003 | | |
| Yes | 51 (44.0) | 142 (61.2) | | 1.97 | 1.18,3.29 |
| No | 65 (56.0) | 90 (38.8) | | | |
| Working as labour in yellow soybean fields | | | 0.339 | | |
| Yes | 16 (13.8) | 27 (11.6) | | 0.40 | 0.41,1.14 |
| No | 100 (86.2) | 205 (88.4) | | | |
| Working as labour in cotton field | | | 0.110 | | |
| Yes | 6 (5.2) | 25 (10.8) | | 2.18 | 0.52,9.20 |
| No | 110 (94.8) | 207 (89.2) | | | |
| Raising animals (dog, pig, goat, sheep and rabbit) | | | 0.001 | | |
| Yes | 85 (73.3) | 96 (41.4) | | 0.16 | 0.02,0.99 |
| No | 31 (26.7) | 136 (58.6) | | | |
| Bundling or moving waste straw | | | 0.008 | | |
| Yes | 22 (19.0) | 76 (32.8) | | 1.42 | 0.77,2.63 |
| No | 94 (81.0) | 156 (67.2) | | | |
| Outdoor related activities | | | | | |
| Morning exercise in the park or field | | | 0.001 | | |
| Yes | 4 (3.4) | 36 (15.5) | | 8.03 | 1.33,48.62 |
| No | 112 (96.6) | 196 (84.5) | | | |
| Risk behaviors | | | | | |
| Dry clothes in the grass | | | 0.30 | | |
| Yes | 5 (4.3) | 27 (11.6) | | 1.66 | 0.30,9.01 |
| No | 111 (95.7) | 205 (88.4) | | | |
| Fishing | | | 0.017 | | |
| Yes | 6(5.2) | 32 (13.8) | | 1.98 | 0.57,6.89 |
| No | 110 (94.8) | 200 (86.2) | | | |
| Having travel history | | | 0.405 | | |
| Yes | 3 (2.6) | 3 (1.3) | | 0.46 | 0.07,2.73 |
| No | 113 (98.3) | 229 (98.7) | | | |

*Computed using Chi-square or Fisher's exact test; Abbreviations: (Odds Ratio& 95%CI, Confidence Interval) are computed using binary logistic regression.

**Table IV: Multivariate logistic regression analysis model of studieda factors associated with ST infection a**

| Variable (s) | Adjusted OR | 95% C.I. |
|---|---|---|
| Age | 1.01 | 0.99, 1.04 |
| Raising animals (dog, pig, goat, sheep and rabbit) | 0.38 | 0.20, 0.71 |
| Houses near grassland, vegetable field or ditch) | 0.39 | 0.19, 0.79 |
| Piling weeds in the yard | 0.15 | 0.07,0.32 |
| Bundling or moving waste straw | 1.94 | 0.99, 3.81 |
| Moring exercise in park or field | 4.74 | 1.19,18.95 |
| Dry clothes in the grass | 2.08 | 0.42, 10.25 |
| labour in vegetable field | 1.80 | 1.02,3.19 |
| Working as labour in yellow soybean fields | 0.29 | 0.10,0.82 |
| Having travel history | 0.28 | 0.05,1.63 |
| Constant | 1.14 | |

[a]Overalldata of the model results based on Hosmer and Lemeshow Test: Chi-square= 6.645; P=0.575; df=8. Abbreviations: OR = Odds ratio; CI = confidence interval.

evidence that 90 (77.6%) of the ST cases group and 187 (80.6%) of the control groups practiced farming activities. Thus, the factors associated with ST infection include living environments, workplace, outdoor agriculture activities, and human behavior. Comparatively, female patients were highly associated with ST infection compared with male subjects.[15] Farmers were exposed to chigger mites mainly because they were involved in agricultural activities.[31]

As evidenced in the living environment, other environmental consequences attributed some of the factors associated with ST to a residential location, living in houses near grassland, vegetable field or ditch, occupation, piling weeds in the yard, and house environment presence of mouse activities.This evidence is consistent with other studies conducted in Vientiane city, where living in neighborhoods with high buildings and close to markets were at greater risk of ST infection.[32] Also, this current research findings support the findings from previous study conducted in Bejing city.[24]

Furthermore, the results showed that places of agricultural labour, outdoor agriculture activities, and human behavior factors were similar to those reported in Korea,[17] Guangzhou,[20] and Beijing.[15] In this study, farmers are high-risk groups of ST infection. In China, outbreaks of ST are typically high among farmers and those living in rural areas.[20] The findings also reported exposure during the last month for the case and control in work, outdoor-related activities, and behaviors.

This study identified that the daily morning exercise in the parks, fishing in the rivers, raising animals (dogs, pigs, goats, sheep, and rabbits), bundling or moving waste straw, working as labourers, especially in the vegetable field, are the main factors that have been significantly associated with the risk of ST exposure. Since the vectors (mites) have high mobility and are widely spread in different vegetation types, grasses, and scrubland, this result is similar to the study conducted in Guangzhou and Beijing, which showed that morning exercise in a park or field or walking in the grassland was also associated factors with ST infection.[20] The current research findings are consistent with other previous studies that reported that cases tend to increase when people are exposed to ST infection during outdoor activities.[15,17,20] This result agrees with the study demonstrating that outdoor agriculture activities were also reported significant findings among cases compared with the control group in Korea.[17] The frequency of having outdoor agriculture activities have increases the factors associated with ST infection among humans[17] and showed protective associations to ST infection.[22]

The case-control method was applied to identify several factors associated with ST infection, and it was observed that there were twice as many reported cases among the farmer-related activities, such as bundling or moving waste straw, working as labour in vegetable fields. Each of these factors isan indicator of the ST risks.

Although this is the first case-control study that was conducted in Luhe District to assess ST infection risk, it is not without limitations. Firstly, data collection was based on a passive surveillance system only, and we used a relatively small sample size for analysis. Second, there was some potential for recall bias due to the methodology approach and the need for respondents to report infection experiences with ST in 2015-2017, which involved are call from a long time for the disease onset to be investigated. Nevertheless, these findings help to establish the screening of high-risk patients with ST infection in the district,which will be further used to improve the health planning and health care policies in the community. It will also facilitate the implementation of adequate health care services to establish for the future in establishing an evidence-based intervention strategy to reduce factors associated with ST infection.


## ACKNOWLEDGEMENT

The authors would like to thank the health staff in Luhe District, Nanjing Municipal Center for Disease Prevention and Control for their participation in this work. The authors would also like to acknowledge all the multidisciplinary members and classmates who highly contributed to data collection and support in completing this study.

## FUNDING

This study was funded by Jiangsu Provincial Social Science Foundation, grant number 13TYA001.


## DISCLOSURE

None

## CONFLICTS OF INTEREST

None

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