

A Community-based Case-control Study of Behavioral Factors Associated with Scrub Typhus during the Autumn Epidemic Season in South Korea

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Abstract. A community-based, case-control study was carried out to investigate risk factors for scrub typhus in South Korea. Cases ($n = 299$) were defined as persons who were diagnosed serologically within the past two weeks. Two neighborhood control subjects were selected by matching for sex, age, and occupation. Taking a rest directly on the grass, working in short sleeves, working with bare hands, and squatting to defecate or urinate posed the highest risks, with adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of 1.7 (1.2–2.3), 1.6 (1.1–2.4), 1.7 (1.2–2.4), and 2.0 (1.4–2.9), respectively. Wearing a long-sleeved shirt while working, keeping work clothes off the grass, and always using a mat to rest outdoors showed protective associations, with aORs and 95% CIs of 0.5 (0.3–0.9), 0.6 (0.4–0.9), and 0.7 (0.5–0.9), respectively. These results might be useful in the establishment of a detailed control strategy for scrub typhus.

INTRODUCTION

Scrub typhus or tsutsugamushi disease is a febrile illness caused by the rickettsial bacterium *Orientia tsutsugamushi*, which is transmitted by the bites of infected, immature mites (chiggers) belonging to the family Trombiculidae and primarily consisting of the genus *Leptotrombidium*. This disease is widely endemic in a geographically confined area of the Asia-Pacific region, the so-called tsutsugamushi-triangle, which includes Nepal and India in the west; Japan, Taiwan, China, and South Korea in the north; and Australia and Indonesia in the south. Countries not endemic for this disease have also reported cases involving visitors to disease-endemic areas.^{1,2}

Most cases in disease-endemic areas occur through agricultural exposure such as working in rice fields in South Korea, Thailand, and Japan, and in oil palm and rubber plantations in Malaysia.³ The most typical complaints of infected persons are fever, headache, rash, eschar, and lymphadenopathy. In some cases, central nervous system symptoms or circulatory collapse caused by disseminated intravascular coagulation can occur, especially in patients with delayed diagnosis.⁴ The clinical course of the disease and the prognosis vary depending on the character of the endemic strain.⁵ Patients with scrub typhus have high fatality rates of up to 50–60% and clinical courses ranging from 10 to 28 days before antibiotics were introduced.^{3,6} Scrub typhus is usually successfully treated with doxycycline, tetracycline, or chloramphenicol, but repellents and chemoprophylaxis have limited efficacy.

The increasing number of outdoor activities performed by urban inhabitants, the rapid urbanization of societies, increasing age of populations, and significant evolution of diagnostic techniques and public surveillance systems may be contributing to the increase of scrub typhus.^{7–9}

Scrub typhus is a public health issue in Asia, where one million new cases are identified annually and one billion people

may be at risk for the disease.¹⁰ In South Korea, scrub typhus is the most common rickettsial disease, with more than 4,500 cases reported annually since 2004, and public health authorities are very aware of its increase. Since 1994, scrub typhus has been a reportable disease in South Korea. Although many studies of scrub typhus have been performed in disease-endemic areas, little attention has been given to behavioral risk factors for the disease.¹¹

Scrub typhus is not transmitted directly from person to person; it is only transmitted by the bites of vectors. Therefore, the health behaviors of persons during outdoor activities are meaningful factors for strategies to control scrub typhus. To identify the kinds of work and behavioral risk and protective factors associated with the incidence of scrub typhus, we undertook a community-based, case-control study.

MATERIALS AND METHODS

Study design and participants. The study area consisted of two metropolitan cities (Gwangju and Daejeon) with populations greater than one million, five cities (Namwon, Nonsan, Masan, Gyeongju, and Yeongcheon), and eight rural communities denoted by “gun” (Changnyung, Haman, Cheongdo, Boseong, Hwasun, Sunchang, Gumsan, and Buyo). The study area comprised five provinces (Jeonnam, Jeonbuk, Chungnam, Gyeongnam, and Gyeongbuk) that are located in the southern part of the Korean peninsula and have shown a high incidence of scrub typhus in recent years (Figure 1).

A case was defined as a reported scrub typhus case diagnosed within the past two weeks using laboratory confirmation (a four-fold increase in the antibody titer in follow-up serum, antigen detected in blood, or genetic material detected using polymerase chain reaction).^{12–14} Eligible controls were defined as neighbors of the case subject who were matched for age (within 4 years), sex, and occupation (farmer or non-farmer) and lacked a history of scrub typhus within two years according to the National Notifiable Disease Surveillance System (NNDSS) of South Korea. If an appropriate matched control was not available in the nearest household, then the next nearest household was chosen. A total of 301 cases and 602

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FIGURE 1. Location of the study area in South Korea and number of local districts that were included in the case-control study.

controls were recruited from the 15 study areas from October through December 2007. More than 97% of total scrub typhus cases were identified in NNDSS of South Korea during a three-month period.¹⁵ Two cases and their four matched controls, who were all less than 10 years old, were eliminated from the final analysis because these persons likely had different lifestyles on the basis of their youth compared with the remaining persons.

Data collection. Scrub typhus has been a reportable disease in South Korea since 1994. Physicians who diagnose suspected or confirmed cases of scrub typhus must report the case to the local health center within seven days. Thus, whenever a serologically confirmed case was reported, the local health bureau passed the case information to our study group by fax or e-mail. Trained interviewers visited the cases and identified matched controls (1:2 pair matching) from their nearest neighbors. We were particularly interested in modifiable behaviors during outdoor activities, such as the type of agricultural work, as well as sanitary habits during and after outdoor activities. The potential confounders of age, sex, and occupation (farming and non-farming) were controlled by matching. A standardized questionnaire was used by trained interviewers to collect detailed information on cases and controls. Three main categories of variables were considered in the questionnaire: socioeconomic status (age, marital status, education level, solitary living, and residential environment), outdoor activities (work places, type of work engaged in within the previous one month in consideration of the incubation period, and delay time from disease onset), and potential risky or protective behaviors during outdoor activities.

We obtained verbal informed consent from all study subjects. This study was reviewed and approved by the Korean Centers of Disease Control and Prevention (KCDC), the governmental agency in charge of communicable disease control in South Korea.

Statistical analysis. Univariate conditional logistic regression test was used to compare the demographic characteristics of cases and controls, and the potential risk or preventive factors for scrub typhus were assessed using a conditional logistic regression model. Consequently, we present odds ratios (ORs)

with the 95% confidence intervals (CIs) of exposure for various factors. We also present the adjusted ORs with the 95% CIs controlling for age and socioeconomic factors such as education level, living alone, and the presence of a shower room in the home. All analyses were conducted using the SAS statistical package version 8.2 (SAS Institute, Cary, NC).

RESULTS

We recruited 299 scrub typhus cases and 598 matched controls. Of the cases, 112 (37.5%) were females and 172 (57.5%) were farmers. The greatest age class in the age distribution was the 60–79 years age group, and this was similar between the two groups.

Demographics. For cases and controls, respectively, 76.9% and 73.6% were married, 16.4% and 17.9% lived alone, 85.3% and 87.6% lived in an independent type house, and 82.9% and 79.1% had an individual shower room in the home. There were no significant differences in demographic characteristics between cases and controls (Table 1).

Places of work and type of outdoor activity. Table 2 shows the crude ORs and adjusted ORs (aORs) for the work places and type of outdoor activity within one month from the onset. Persons who had worked in orchards, livestock yards, and forests within one month had significantly higher risk than did other persons. The adjusted ORs (95% CI) for dry field, orchards, livestock yards, and forests were 1.5 (1.2–2.0), 1.9 (1.1–3.3), 2.3 (1.3–3.9), and 3.3 (2.1–5.1), respectively, adjusting for age, education level, marital status, solitary living, and having a shower room. For work in dry fields, these differences were only present in women after stratification by sex,

TABLE 1
Demographic characteristics of the scrub typhus cases and controls in South Korea that were enrolled in the study

Characteristic	Case (n = 299)		Control (n = 598)		P
	No.	%	No.	%	
Sex					–
Male	112	37.5	224	37.5	
Female	187	62.5	374	62.5	
Occupation					–
Farmer	172	57.5	344	57.5	
Non-farmer	127	42.5	254	42.5	
Residential district					–
Rural	227	75.9	454	75.9	
Urban	72	24.1	144	24.1	
Age group, years					0.644
20–39	22	7.4	40	6.7	
40–59	83	27.8	165	27.6	
60–79	181	60.5	368	61.5	
≥ 80	13	4.3	25	4.2	
Education, years					0.268
≤ 6	186	62.4	396	66.2	
> 6	112	37.6	202	33.8	
Marital status					0.363
Married	230	76.9	440	73.6	
Divorce/unmarried	69	23.1	158	26.4	
Lived alone					0.662
Yes	49	16.4	107	17.9	
No	250	83.6	491	82.1	
Housing type					0.230
Independent	255	85.3	524	87.6	
Apartment/others	44	14.7	74	12.4	
House with a shower room					0.292
No	51	17.1	125	20.9	
Yes	247	82.9	472	79.1	

TABLE 2
Associations between outdoor activities and risk behaviors in outdoor activities within the previous month from onset and scrub typhus, South Korea*

Exposure within one month	Case (n = 299) No. (%)	Control (n = 598)† No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)‡
Places of work				
Rice field	115 (38.5)	259 (43.3)	0.8 (0.6–1.1)	0.8 (0.5–1.1)
Dry field	203 (67.9)	332 (55.5)	1.4 (1.1–1.8)	1.5 (1.2–2.0)
Orchard	46 (15.4)	63 (10.5)	1.9 (1.1–3.0)	1.9 (1.1–3.3)
Livestock yard	38 (12.7)	44 (7.4)	2.1 (1.3–3.6)	2.3 (1.3–3.9)
Vinyl greenhouse	24 (8.0)	34 (5.7)	1.5 (0.9–2.7)	1.5 (0.9–2.8)
Forest	84 (28.1)	99 (16.6)	2.9 (1.9–4.5)	3.3 (2.1–5.1)
Outdoor activities				
Mowing around graves	58 (19.4)	109 (18.2)	1.1 (0.7–1.7)	1.1 (0.7–1.8)
Mowing around rice fields	90 (30.1)	199 (33.3)	0.8 (0.6–1.2)	0.8 (0.6–1.2)
Weeding dry fields	81 (27.2)	190 (31.8)	0.7 (0.5–1.0)	0.7 (0.5–1.1)
Harvesting in rice fields	97 (32.4)	209 (34.9)	0.9 (0.6–1.2)	0.9 (0.6–1.3)
Harvesting in dry fields	166 (55.5)	289 (48.3)	1.6 (1.1–2.1)	1.6 (1.1–2.4)
Harvesting fruits	42 (14.0)	57 (9.5)	1.9 (1.1–3.3)	1.9 (1.1–3.3)
Gathering chestnuts	72 (24.1)	80 (13.4)	2.3 (1.5–3.3)	2.2 (1.5–3.3)
Leisure activities§	35 (11.7)	118 (19.8)	0.5 (0.3–0.8)	0.4 (0.3–0.7)

* OR = odds ratio; CI = confidence interval.
 † Matched by age, sex, occupation, and residential district.
 ‡ Adjusted for age, education level, marital status, solitary living, and having a shower room.
 § Leisure activities involved fishing, climbing, golf, picnicking, and camping.

and the OR (95% CI) of males and females was 0.9 (0.5–1.5) and 3.4 (2.1–5.7), respectively. No significant differences were observed in cases that involved work in rice fields or vinyl greenhouses. Persons who had engaged in harvesting activities in dry fields or who had harvested fruits or gathered chestnuts in the mountains had a significantly higher risk of scrub typhus infection with aORs (95% CIs) of 1.6 (1.1–2.4), 1.9 (1.1–3.3), and 2.2 (1.5–3.3), respectively. Leisure activities such as fishing, climbing, golf, picnicking, and camping were negatively associated with infection risk and had an aOR (95% CI) of 0.4 (0.3–0.7). This negative association disappeared in non-farmers in the analysis after stratification by occupation and was maintained only in the farmers.

Risk and protective behaviors. In the adjusted model, resting on a grass field without a mat (aOR = 1.7, 95% CI = 1.2–2.3), a history of working in short sleeves (aOR = 1.6, 95% CI = 1.1–2.4), working with bare hands (aOR = 1.7, 95% CI = 1.2–2.4), defecating outdoors while squatting (aOR = 2.0, 95% CI = 1.4–2.9), and urinating on the grass (aOR = 1.5, 95% CI = 1.1–2.1) yielded significantly increased risk for scrub typhus (Table 3). Of the protective behaviors, wearing a long-sleeved shirt, not placing a work uniform on the grass, and always using a mat while resting outdoors instead of sitting on the bare ground or grass were negatively associated with infection risk and had aORs (95% CI) of 0.5 (0.3–0.9), 0.6 (0.4–0.9), and 0.7 (0.5–0.9), respectively (Table 3). The use of insect repellents and health education for scrub typhus were not significantly associated with its occurrence.

DISCUSSION

We examined the association between scrub typhus infection and work-related behavioral factors using a community-based, case-control study. To our knowledge, the only comparable study is that of Kim and others, who used a similar case-control design and found associations between scrub typhus and fruit farming, gathering chestnuts, and health education.¹¹ The main differences between our work and their work are that we used age- and sex-matched controls, new cases diagnosed within the past two weeks, and persons recruited from all

disease-endemic areas of South Korea. Therefore, selection and recall bias were less likely to affect our results.

Although rice farmers are considered to be a high-risk group for scrub typhus,^{3,6} the association has not been clarified in detail. Although we found no associations of scrub typhus infection with rice-farm-related factors, there were strong positive associations with dry-field-related factors. Persons who had worked in dry fields within the previous month, especially women, and persons who had performed harvesting activities in dry fields were at increased risk for scrub typhus. In South Korea, farmers in dry fields typically work in a squatting posture with bare hands and are usually women, whereas rice field workers generally stand while working, use instruments, and are men. Furthermore, dry fields are located adjacent to mountains, and rice fields are located near rivers. Therefore, workers in dry fields, especially women, are more likely to be exposed to infected mites. Another possible reason for the significant association with dry fields, but not rice fields, was that 95% of the study participants were interviewed after November 10; by this date, work in the rice fields has generally ended. In contrast, work in dry fields usually continues into November and includes the harvesting of beans, capsicum, and other crops.

Leptotrombidium palladium, the predominant mite species in South Korea, begins to appear in September and has a peak population in October–November.¹⁶ Thus, study participants were less likely to engage the rice-field related work than dry-field-related work during the previous month and usually finished their work in rice fields before the peak infestation period.

Farm and forest workers are well known to be high-risk groups. We found strong positive associations with orchard, livestock yard, and forest work; persons who had harvested fruit in orchards or had gathered chestnuts in the forest within the previous month also showed a high risk for scrub typhus. The negative association with leisure activities can be explained by a protopathic (or reverse-causality) bias. The case subjects might have had less leisure time than the controls because of the illness caused by scrub typhus infection or the time-demanding nature of agricultural work. As described

TABLE 3

Associations between risk and protective behaviors during outdoor activities within the previous month from onset and scrub typhus, South Korea*

Exposure within one month	Case (n = 299) No. (%)	Control (n = 598)† No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)‡
Risk behaviors				
Working directly after raining	46 (15.4)	106 (17.7)	1.2 (0.8–1.8)	1.2 (0.8–1.8)
Eating lunch or a snack outdoors	101 (33.8)	183 (30.6)	1.2 (0.9–1.6)	1.2 (0.9–1.7)
Resting on a grass field	175 (58.5)	290 (48.5)	1.6 (1.2–2.2)	1.7 (1.2–2.3)
Taking a nap on grass field	15 (5.0)	31 (5.2)	1.0 (0.5–1.9)	0.9 (0.5–1.8)
Working in short sleeves	60 (20.1)	90 (15.1)	1.5 (1.0–2.2)	1.6 (1.1–2.4)
Working with bare hands	120 (40.1)	176 (29.4)	1.8 (1.3–2.5)	1.7 (1.2–2.4)
Squatting to defecate	136 (45.5)	212 (35.5)	1.7 (1.3–2.5)	2.0 (1.4–2.9)
Urinating on the grass	154 (51.5)	264 (44.1)	1.5 (1.1–2.0)	1.5 (1.1–2.1)
Protective behaviors				
Wear a long-sleeved shirt	246 (86.6)	474 (91.5)	0.6 (0.4–0.9)	0.5 (0.3–0.9)
Shower/bathe	180 (63.4)	342 (66.0)	0.8 (0.6–1.2)	0.8 (0.6–1.2)
Changing a uniform	209 (73.6)	415 (80.1)	0.7 (0.5–1.0)	0.7 (0.5–1.1)
Do not place a uniform on the grass	184 (64.8)	358 (69.8)	0.7 (0.5–1.0)	0.6 (0.4–0.9)
Work with gloved hands	187 (65.8)	367 (70.8)	0.8 (0.5–1.2)	0.8 (0.5–1.1)
Wear socks while working	269 (94.7)	488 (94.2)	1.0 (0.5–2.1)	0.9 (0.5–2.0)
Use a mat to rest	102 (35.9)	220 (42.5)	0.7 (0.5–0.9)	0.7 (0.5–0.9)
Use insect repellents	5 (1.7)	16 (2.7)	0.6 (0.2–1.7)	0.6 (0.2–1.8)
Receiving health education	8 (2.7)	22 (3.7)	0.7 (0.3–1.6)	0.7 (0.3–1.7)

* OR = odds ratio; CI = confidence interval.

† Matched by age, sex, occupation, and residential district.

‡ Adjusted for age, education level, marital status, living alone, and having a shower room.

previously, this negative association disappeared in non-farmers after stratification according to occupation.

Our results suggest that workers who tend to expose their skin during outdoor activities are vulnerable to scrub typhus infection. In addition, preventive behaviors that reduce exposure to infected mites, e.g., wearing a long-sleeve shirt, not placing a work uniform on the grass, and always using a mat to rest outdoors instead of resting on the bare field or grass, had significant negative associations with scrub typhus infection in unadjusted and adjusted models. The education level of participants, environment of the area of residence or house, and possession of pets or domestic animals were not associated with the disease.

Only 2.3% and 3.3% of the participants had used insect repellents and received prevention education for scrub typhus during their lifetimes, respectively. Therefore, the efficacy of these measures for preventing scrub typhus was not clearly evaluated. The KCDC recently began to dispense insect repellent and to perform an intensive health education program in disease-endemic areas. Thus, a prospective study is required in these regions to investigate the efficacy of these two prevention measures.

Our study has specific strengths. First, the study was representative of the South Korean population because of the use of community-based study participants. Second, the potential for recall bias was small because of the use of newly reported cases. Third, the results have definite implications for public health because the study targeted modifiable behaviors. Furthermore, to ensure comparability between the case and control groups, all participants in each neighborhood that had the same occupation were interviewed by the same interviewer on the same day.

Our study also had limitations. First, the interviewers were not blinded to the case-control status of the participants. Second, because we failed to identify the transmission mode in each case, we could not verify the role of the risk factors in the real transmission process. Third, the sample size was relatively small considering the heterogeneity of the study participants. Consequently, we could not identify a relationship

between the frequency of the risk factors and the occurrence rate of infection. The neighborhood-matched design may have made cases and control participants similar for certain variables, such as occupation or residential area, and possibly work place. Although conditional logistic regression was performed, overmatching may have affected the precision of OR estimates.¹⁷

Despite these limitations, our study presents worthy results that can contribute to the establishment of an evidence-based intervention strategy to reduce the incidence of scrub typhus. Outdoor activities and working habits that make a person vulnerable to infection and protective behaviors were ascertained. Thus, our findings will be helpful in the establishment of a detailed intervention program to control scrub typhus in all disease-endemic countries.

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