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Scrub typhus in Darjeeling, India: opportunities for simple, practical prevention measures☆

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Summary To identify risk factors for scrub typhus in Darjeeling, India, we compared 62 scrub typhus cases (acute fever with eschar and specific IgM) with 62 neighbourhood controls. Cases were more likely to live close to bushes [matched odds ratio (MOR) 10; 95% CI 2.3—63] and wood piles (MOR 3.5; 95% CI 1.5—9.5), to work on farms (MOR 10; 95% CI 2.7—63), to observe rodents at home (MOR 3.6; 95% CI 1.4—11) and at work (MOR 9; 95% CI 2.4—57), and to rear domestic animals (MOR 2.4; 95% CI 1.1—5.7). Cases were less likely to wash after work (MOR 0.4; 95% CI 0.1—0.9) and change clothes to sleep (MOR 0.2; 95% CI 0.1—0.5). A cleaner, rodent-controlled environment may prevent exposure to scrub typhus. Personal protection measures and better hygiene could further reduce individual risk.

1. Introduction

Scrub typhus is an acute, zoonotic, febrile illness of humans.[1] The etiological agent, *Orientia tsutsugamushi*, is transmitted through the bite of infected mites (actually, the larval stage, known as chiggers).[1,2] The mites normally feed upon single vertebrate hosts, usually rodents.[3] Foci of scrub typhus (typhus or mite islands) have been reported.[4] Fever typically begins 6—21 days following the bite and is accompanied by a maculopapular rash, headache and lymphadenopathy.[5] A typical focal lesion or eschar may develop at the bite site.[1] The treatment of choice is doxycycline.[6]

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Scrub typhus is widespread, extending from Japan to Australia and from India to the Pacific. The disease has been reported from seashores, mountainous regions, rainforests, semi-arid deserts, river banks and terrain undergoing secondary vegetation growth.[7] Most cases occur through agricultural exposure.[7] Scrub typhus has been reported in the Asia-Pacific region since the Second World War.[8–11] In India, it has been reported in the east, south and the Himalayas.[12–14]

Kurseong sub-division is located in the Darjeeling district of West Bengal, India, at the foot of the Himalayas. In 1969, *Leptotrombidium deliense*, a mite vector, was reported among rats in the district up to altitudes of 3840 m.[15] However, there were no reports of scrub typhus. In 2000, patients with fever of unknown origin were admitted to Kurseong hospital. Of these, some died of multi-organ failure. Until 2003, similar cases continued to occur, particularly between June and October (the rainy season). The absence of laboratory diagnostic facilities prevented the identification of an etiological agent. In 2004, a new cluster of patients presenting with a typical eschar led to the suspicion of scrub typhus, which was supported by the results of Weil-Felix tests. Although the disease was now recognized, lack of information on local risk factors prevented the formulation of specific recommendations. In 2005, we conducted a case-control study to estimate the strength of the association between selected exposures and scrub typhus, to estimate the fraction of cases attributable to the selected exposures and to estimate the fraction of cases of scrub typhus that could be prevented through personal protection measures.

2. Methods

We defined the study population as the residents of Kurseong sub-division of Darjeeling district, West Bengal, India. We conducted a case-control study with two control groups, one matched, community-based and one unmatched, hospital-based.

2.1. Cases and controls

We defined a case of scrub typhus as an acute onset of fever >38 °C with eschar and laboratory confirmation of IgM antibody specific for scrub typhus at $\geq$1:128 titre by an IFAT in a patient admitted to Kurseong hospital in 2005. We recruited all cases meeting the clinical case definition during the study period. For the matched control group we recruited one healthy neighbour per case, matched for age. For the unmatched, hospital-based control group we recruited patients suffering from typhoid (confirmed by the Widal test with a four-fold rise in 'O' antibody titre, blood samples taken 10 days apart) in the same hospital at the same time.

2.2. Laboratory investigations

To confirm the diagnosis we used blood samples collected from scrub typhus and typhoid patients as part of routine hospital procedures for their treatment. A qualified laboratory technician collected 10 ml of blood by venepuncture using sterile disposable equipment. We sent the specimens to the National Institute of Communicable Diseases, New Delhi, India for estimation of the titre of IgM antibodies to scrub typhus (micro-immunofluorescence format based on IFAT, Australian Rickettsial Reference Laboratory). We used cut-off IgM titres $\geq$1:128 as positive for scrub typhus on the basis of an assessment of a group of controls from the area that included fever patients with other diagnoses and healthy persons.

2.3. Data collection

We collected information on demographic characteristics, place of residence, activities (including occupation) as well as exposure to forests, bushes, domestic animals, rodents and ectoparasites. We defined the referent exposure period as the 21 days prior to the appearance of clinical signs and symptoms (for cases and hospital-based controls) or prior to recruitment (for neighbours). We trained health personnel to conduct interviews using structured, standardized, closed-ended, pre-tested questionnaires written in Nepali, the local language.

2.4. Sample size

Assuming an exposure prevalence of 10% among controls and aiming at detecting odds ratios of at least three with a 95% confidence interval and 80% power, we needed to recruit 112 cases and 112 controls. To allow for non-responses we planned a sample size increase of 10%. Thus, our target was to recruit 123 cases and 123 controls in each of the control groups.

2.5. Data analysis

We described the incidence of scrub typhus in terms of time, place and person for the year 2005 using census data as denominators. We calculated matched odds ratios (MOR) using discordant pairs for all exposures for the neighbourhood control group. We calculated unmatched odds ratios (OR) for all exposures for the hospital-based control group. We calculated the fraction of cases attributable to various exposures in the population (AFP) when causality was suspected: $\text{AFP} = \text{proportion of cases exposed} \times [(\text{OR}-1)/\text{OR}]$. For exposures associated with a lower risk of illness, we calculated the fraction of cases attributable to the failure to use the prevention measure. We stratified to eliminate confounding and to identify effect modifiers. After checking that the matched and unmatched odds ratios for some significant exposures were similar, we broke the match and examined the dose-response relationship by calculating the odds ratios according to increasing gradients of exposure. We analyzed the data using EpiInfo 2005 (CDC, Atlanta, GA, USA). A *P*-value of 0.05 was considered statistically significant.

2.6. Human subject protection

Our study did not affect the routine clinical practice of the hospital. We explained the objectives, methods, risks

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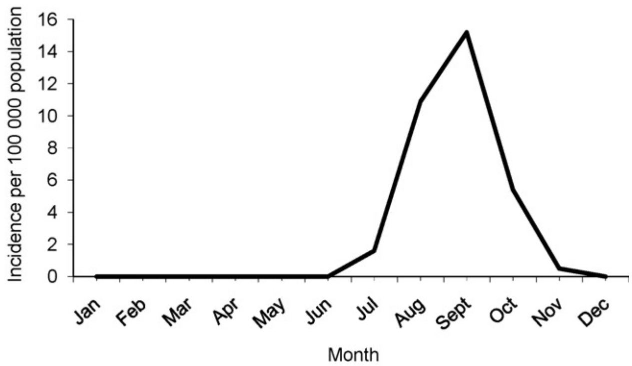

Figure 1 Incidence of scrub typhus cases by month of occurrence in Kurseong, Darjeeling district, West Bengal, India, 2005.

and benefits of the study to the participants and took written informed consent. We used confidential codes and approached healthy neighbourhood controls using precautions to maintain the confidentiality of the matched cases.

3. Results

3.1. Descriptive epidemiology

The incidence of scrub typhus increased from 2 per 100 000 population in July 2005 to 20 per 100 000 population in September 2005 and then decreased to zero in December (Figure 1). The overall incidence in Kurseong sub-division was 34 cases per 100 000 population. Scrub typhus clustered in some rural, agricultural areas (e.g. tea plantations) but there were no outbreaks. Females had a higher incidence than males. The age group 30—44 years had the highest incidence (79 per 100 000 population; Table 1).

3.2. Laboratory investigations

Of 122 cases meeting the clinical case definition for scrub typhus and whose blood samples were sent for laboratory confirmation, 62 (51%) were positive. Fifty-two typhoid cases were confirmed by a four-fold rise in antibody titre using paired sera.

3.3. Characteristics of cases and controls

We included 62 scrub typhus patients in the case-control analysis. We recruited 62 healthy, matched, neighbourhood controls and 52 unmatched, typhoid controls. Compared to matched controls, cases were more likely to be female and more likely to belong to the general (upper) caste. Compared to unmatched controls, cases were less likely to reside in wooden houses and belong to the general (upper) caste. However, none of these differences was statistically significant (Table 2).

3.4. Living environment

In the unmatched analysis, the presence of piles of wood in the yard of the house was the only environmental characteristic significantly associated with illness (Table 3). The association between illness and exposure to rodents at home was stronger among those rearing animals in the yard (OR 5.6; 95% CI 1.8—20) than among others (OR 2.1; 95% CI 0.4—16). Similarly, the association between exposure to bushes close to the house was stronger among those with a monthly family income of more than Rs1500 (US$30) (OR 13; 95% CI 2.5—95) than among others (OR 2.6; 95% CI 0.6—12). Compared with matched controls, cases were more likely to live in environments with bushes, piles of wood, rodents and domestic animals. The odds of disease increased with the number of bushes located within 5 m of the residence and the number of piles wood in the yard of the house (Table 4).

3.5. Activities and occupation

Compared to matched and unmatched controls, cases were more likely to be farmers (Table 3). However, the association was not significant in the unmatched analysis.

3.6. Exposure to vectors

Compared with matched controls, cases were more likely to report itching; however, there was no association between itching and illness in the unmatched analysis (Table 3). The association with itching was stronger among those rearing animals (OR 12; 95% CI 1.3—300) than among others (OR 2.5; 95% CI 0.8—7.8).

Table 1 Incidence of scrub typhus cases by age and gender, Kurseong, Darjeeling, West Bengal, India, 2005

Characteristic	Population	Cases (*n*)	Attack rate per 100 000 population
Age group (years)			
0—4	19 287	5	26
5—14	45 737	10	22
15—29	54 003	16	30
30—44	26 450	21	79
45—59	28 287	10	35
≥60	9 920	0	0
Gender			
Male	97 353	28	29
Female	86 331	34	39
Total	183 684	62	34

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Table 2 Characteristics of scrub typhus cases and controls, Kurseong, Darjeeling district, West Bengal, India, 2005

Characteristic	Cases ($n = 62$)	Unmatched controls, hospital ($n = 52$)		Matched controls, neighbourhood ($n = 62$)	
	n (%)	*n* (%)	*P*-value	*n* (%)	*P*-value
Age ≤30 years	31 (50)	27 (52)	0.9	29 (47)	0.3
Female gender	34 (55)	28 (54)	0.9	38 (61)	0.5
Follower of Hinduism	47 (76)	40 (77)	0.9	49 (79)	0.4
Belonging to general (upper) caste	43 (69)	39 (75)	0.6	40 (65)	0.6
Residence in rural area	52 (84)	44 (85)	0.9	52 (84)	NA
Residence in houses made of wood	45 (73)	42 (81)	0.4	48 (77)	0.4
Monthly income less than Rs1500 (US$30)	30 (48)	25 (48)	0.9	28 (45)	0.8
Household with >4 members	40 (65)	35 (67)	0.9	35 (56)	0.5

Table 3 Selected exposures for scrub typhus cases and controls, Kurseong, Darjeeling district, West Bengal, India, 2005

Exposure		Cases ($n = 62$)	Unmatched controls, hospital ($n = 52$)		Matched controls, neighbourhood ($n = 62$)	
		n (%)	*n* (%)	OR[a] (95% CI)	*n* (%)	MOR[b] (95% CI)
Living environment	Bushes within 5 m	56 (90)	45 (87)	1.4 (0.4–4.6)	38 (61)	10.0 (2.3–63)
	Piles of wood in the yard	39 (63)	21 (40)	2.5 (1.2–5.4)	24 (39)	3.5 (1.5–9.5)
	Rodents seen at home	55 (89)	50 (96)	0.3 (0.0–1.5)	42 (68)	3.6 (1.4–11)
	Rodents seen at work	51 (82)	42 (81)	1.1 (0.4–2.9)	35 (56)	9.0 (2.4–57)
	Domestic animals in the yard	44 (71)	39 (75)	0.8 (0.3–1.8)	33 (53)	2.4 (1.1–5.7)
Activities	Plucking tea leaves	10 (16)	7 (13)	1.2 (0.4–3.7)	9 (15)	1.2 (0.4–4.3)
	Working in a farm	44 (71)	32 (61)	1.5 (0.7–3.4)	26 (42)	10.0 (2.7–63)
	Working in the forest	15 (24)	18 (35)	0.6 (0.2–1.3)	23 (37)	0.5 (0.2–1.1)
	Working at construction sites	6 (10)	1 (2)	5.3 (0.8–13)	5 (8)	1.2 (0.4–4.3)
Exposure to vectors	Presence of ticks/lice on the body	15 (24)	22 (42)	0.4 (0.2–1)	10 (16)	1.6 (0.7–4.1)
	Itching	25 (40)	22 (42)	0.9 (0.4–2)	11 (18)	3.0 (1.3–7.6)
Hygiene and protective practices	Wearing gumboots at work	23 (37)	27 (52)	0.5 (0.2–1.2)	36 (58)	0.5 (0.2–0.9)
	Washing/bathing after daily work	45 (73)	47 (90)	0.3 (0.1–0.8)	56 (90)	0.4 (0.1–0.9)
	Wearing aprons at work	5 (8)	4 (8)	1 (0.2–4.6)	13 (21)	0.3 (0.1–0.9)
	Changing clothes to sleep	27 (44)	38 (73)	0.3 (0.1–0.6)	51 (82)	0.2 (0.1–0.5)
	Using mite repellents on body	4 (6)	1 (2)	3.5 (0.4–18)	5 (8)	0.8 (0.2–3.2)
	Using mite repellents on clothes	5 (8)	2 (4)	2.2 (0.4–17)	3 (5)	1.7 (0.4–8.5)

[a] Odds ratio.
[b] Matched odds ratio.

Table 4 Odds of scrub typhus according to increasing gradients of exposure to selected risk factors, Kurseong, Darjeeling district, West Bengal, India, 2005

Exposure	Cases ($n = 62$) *n* (%)	Controls ($n = 62$) *n* (%)	Odds ratio (95% CI)
Bushes within 5 m of house[a]			
None	6 (10)	24 (39)	1
1–6 bushes	24 (39)	26 (42)	3.7 (1.1–12)
>6 bushes	32 (52)	12 (19)	11 (3.1–38)
Piles of wood in the yard[b]			
None	23 (37)	38 (61)	1
1–2 piles	29 (47)	19 (31)	2.4 (1–5.7)
>2 piles	11 (18)	5 (8)	3.6 (1–14)

[a] χ^2 for trend: 19.8; *P*-value: <0.001.
[b] χ^2 for trend: 7.4; *P*-value: 0.006.

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3.7. Hygiene and protective measures

Compared with both sets of controls, cases were less likely to wash after work and to change clothes to sleep (Table 3). Compared with matched controls, cases were less likely to wear gumboots and aprons (Table 3). The use of repellents did not exceed 8% among cases and controls. There was no association between this practice and illness. The association between changing clothes to sleep and decreased odds of disease was stronger among those earning more than Rs1500 (US$30) (OR 0.05; 95% CI 0.01—0.3) than among others (OR 0.4; 95% CI 0.1—1.2). Failure to change clothes to sleep, wear gumboots at work and wash after daily work accounted for 45%, 31% and 16% of cases in the population, respectively.

4. Discussion

Exposure to environmental factors including bushes, piles of wood, domestic animals and rodents were significantly associated with illness. Peridomestic rodents may lead to exposure to scrub typhus because they harbour the trombiculid mites that carry the disease. In Palau, households frequented by rodents were more affected by scrub typhus.[16] Bushes and piles of wood are natural habitats of rodents.[4,10,17] Two explanations may account for the association between rearing animals and scrub typhus. First, the storage of fodder for domestic animals may attract rodents[4] and, second, domestic animals might harbour the mites.[17,18] Farmers had higher odds of disease, which may be explained by exposure to rodents, wood piles and animals.[10,16] A study in Japan reported that 44% of patients engaged in farming.[19] A clean living-environment and control of rodents decreased the incidence of scrub typhus significantly among troops in China.[20] Exposure to lice and ticks was a risk factor in our study. These visible ectoparasites do not spread the pathogen by themselves; however, they may constitute a surrogate marker for exposure to the trombiculid mites, which are not easily visible to the naked eye.

Aprons and gumboots, unlike gloves, were associated with a lower risk of illness. Unfed *Leptotrombidium* mites tend to aggregate closely in clusters on twigs and debris a few inches above the ground.[21] The mites are, thus, mostly close to the ground, corresponding with the observation that eschars are more commonly found on the lower part of the bodies of patients. By contrast with changing clothes after work, changing clothes to sleep decreased the risk of scrub typhus. This difference may be explained by the longer period of time available during the night for the mite to bite. Transfer of *Orientia tsutsugamushi* from an infected mite to a human takes more than 6 h.[19] Bathing after work was also associated with a lower risk of illness. Once they gain access to the body the mites seek out areas where clothing is tight against the skin, the parts most commonly attacked being the waist and ankles. They remain attached to the skin of the host for 36—72 h, after which they disengage and drop off onto the ground.[21] Hence, thorough scrubbing and washing of the body after exposure may decrease the risk of bites and, thus, the risk of scrub typhus.[19] While washing and bathing in Kurseong might not systematically include thorough scrubbing, our results suggest some effectiveness of the local hygienic practices.

Our study had several limitations. First, we recruited cases from the hospital and, thus, patients with milder disease in the community may have been excluded. As a result, the study could be biased if patients with more severe disease had a different risk-factor profile. However, there is no evidence suggesting that the number of bites or that the infectious dose influences the natural history of the disease. In addition, among our patients, the severity of the cases did not vary with the number of eschars. Hence, severe cases are likely to be representative of all cases with respect to exposure, and bias is unlikely to have occurred. Second, the study was conducted in Kurseong and the findings may not be generalizable to other places. Thus, our findings regarding environmental factors may be specific to the Darjeeling ecosystem. However, the protective behaviours that we identified, including wearing gumboots at work, washing after daily work and changing clothes to sleep might be generalizable to other areas. Third, less than 8% of participants used repellents. A statistical power calculation suggested that our sample size for that specific, uncommon exposure would not have had a power of 80% to detect an odds ratio of 0.01. Hence, we did not have the capacity to document an association between the use of repellents and scrub typhus. An intervention study may provide a better setting in which to examine the effect of repellents against scrub typhus. Fourth, although our target sample size was 123, we could recruit only 62 cases because the serum samples of the remaining 61 patients were negative for IgM antibody. This low proportion of confirmed disease may be due to the low sensitivity of the test (84% at a cutoff IgM antibody titre of $\geq$1:100 for diagnosis of scrub typhus).[22] Furthermore, collection of blood samples early in the first week of illness and the effects of early chemotherapy following clinical diagnosis might have delayed the appearance of diagnostic titres of IgM antibody.[23] While the recruitment of a smaller number of cases is likely to have reduced the power of our study, the lack of power would not have affected the risk factors and protective practices that we identified. Fifth, since the Widal test is of low sensitivity and specificity, we might have included scrub typhus patients who did not have an eschar and who presented with a false-positive Widal test among the unmatched hospital control group. This would have led to a non-differential misclassification that would have reduced the strength of the association for this control group. However, this would not have prevented us from making conclusions about the risk factors identified as significant.

On the basis of the findings of our study we can propose a number of recommendations for local health authorities and municipalities. Education of the population could make the living and working environments safer with respect to scrub typhus. This would address the clearing of bushes, keeping wood and animals away and controlling rodents. These environmental interventions could be guided by the spatial distribution of the disease so that 'mite islands' are cleared. Promotion of protective measures may reduce individual risks. These include wearing gumboots to work, washing after work and changing clothes to sleep. Further studies could characterize the exact vectors and hosts involved. Behavioural intervention studies could also examine the introduction of safer practices, including repellent use. Finally, hospital-based public-health surveillance will provide an opportunity to evaluate the effectiveness of the proposed prevention measures.

Authors' contributions: MDG, PM and PKS conceived the study; PKS, RR, AKB, MK, VM and YJFH designed the protocol; PKS and AKB collected the data and conducted the analysis and interpretation of the data under the supervision of RR, PM, YJFH and MDG under the Indian Field Epidemiology Training Programme; MK and VM managed the laboratory testing component; PKS and YJFH drafted the manuscript. All authors read and approved the final manuscript. PKS and RR are guarantors of the paper.

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Conflicts of interest: None declared.

Ethical approval: The ethical committee of the National Institute of Epidemiology under the Indian Council of Medical Research approved the final protocol, instruments and consent forms.

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