Preliminary findings of a seroepidemiological survey of arthropod-borne rickettsioses in Malaysia

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Abstract

A total of 609 febrile patients from 7 localities in Malaysia was examined for infection with scrub, tick and murine typhus, by the Indirect Immunoperoxidase Test. Based on IgG titers, tick typhus was the most prevalent (33.7 ± 24.5) followed by scrub (27.3 ±23.9) and murine typhus (20.6 ± 22.1). Single infections occurred only in 40% of cases; mixed infections of tick and murine typhus were the most common. Generally there was no significant association between prevalence and ethnicity, age, sex, as well as occupation. Further studies on the pathogen-host-vector relationship of these 3 rickettsial infections should be undertaken.

Key Words: scrub typhus; murine typhus; tick typhus; typhus prevalence

Introduction

Various arthropod-borne rickettsial infections have been reported in Malaysia. The most well-known and well-studied is scrub typhus which is caused by the organism *Rickettsia tsutsugamushi*. Scrub typhus was first noted in the Federated Malay States in 1915 (Dowden, 1915) and is endemic in Malaysia. A study in Mentakab, a rural district in Malaysia, demonstrated that as many as 23% of fevers were due to scrub typhus (Brown *et al.*, 1976). Based on early serological surveys, it was estimated that as many as 500,000 cases of scrub typhus per year, may occur in Peninsular Malaysia (Saunders *et al.*, 1980).

Serological evidence of tick typhus (antigenically related to the unclassified TT118 rickettsia of the spotted fever group) in wild rodents and humans, was reported in Malaya in the late 1950s (IMR, 1955; 1959; 1960), and by Marchette (1966). Little is known about the present prevalence of this rickettsial infection in Malaysia.

Murine typhus due to *Rickettsia typhi* is also referred to as urban, flea-borne, and endemic typhus. Its presence in Malaya was conclusively demonstrated by Lewthwaite and Savoor (1936a; b; c). In 1951, an active focus of urban typhus in Kuala Lumpur city was reported (IMR, 1951). Another survey showed that murine typhus activity occurred in domiciliated animals living in close association with man (Marchette, 1966). As with tick typhus, the prevalence of the disease in the local human population is still largely unknown.

This study was undertaken with the main aim of determining the sero-prevalence of the above rickettsial infections among febrile patients from selected rural localities in Malaysia. The information obtained will be useful for formulating effective management programmes.

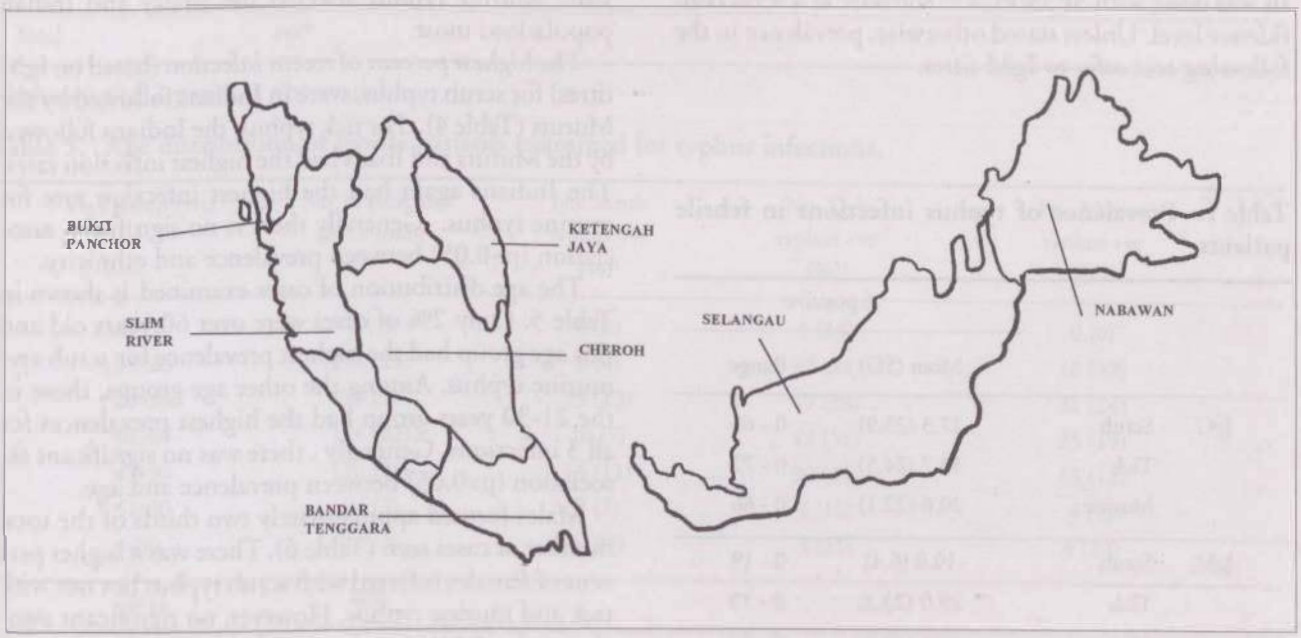

Fig. 1. Location of study sites for seroprevalence of scrub, tick and murine typhus in Malaysia.

Materials and Methods

Study areas

Seven localities in different parts of Malaysia were included in the study, these being Bandar Tenggara (Johore), Bukit Panchor (Pulau Pinang), Slim River (Perak), Cheroh (Pahang), Ketengah Jaya (Terengganu), Selangau (Sarawak), and Nabawan (Sabah) (Fig. 1). These localities are generally rural and close to secondary forest, oil palm and/or rubber plantations. These habitats are known to be associated with scrub and tick typhus.

Cases

Based on various information, it was decided that every fourth febrile patient attending government health clinics in each of the localities above, were selected. The numbers of patients studied in Bandar Tenggara, Bukit Panchor, Slim River, Cheroh, Ketengah Jaya, Selangau and Nabawan were 128, 86, 108, 63, 51, 124, and 49 respectively. Sera from 609 patients were obtained for laboratory investigations and their personal data were recorded.

Laboratory investigations

Sera of patients were sent to the respective State Vector-borne Disease Control Programme (VBDCP) laboratories except for Cheroh, where samples were sent to the Raub Hospital laboratory. Sera were examined by the Indirect Immunoperoxidase Test (IIPT) as described by Kelly *et al.* (1988). Specific IgG and IgM titres were determined and ritres equal or greater than 1:50 were considered positive (Strickman *et al.*, 1994).

Statistical analyses

The degree of association between various variables was determined by chi-square analysis. All statistical analysis was done with SPSS/PC+™ software at a 95% confidence level. Unless stated otherwise, prevalence in the following text refer to IgM titres.

Table 1. Prevalence of typhus infections in febrile patients.

		% positive	
		Mean (SD)	Range
IgG	Scrub	27.3 (23.9)	0 - 65
	Tick	33.7 (24.5)	0 - 72
	Murine	20.6 (22.1)	0 - 66
IgM	Scrub	10.0 (6.4)	0 - 19
	Tick	29.0 (23.2)	0 - 73
	Murine	16.4 (19.0)	0 - 57

Results

The overall prevalences of the 3 infections based on IgM and IgG titres are shown in Table 1. All cases from Bandar Tenggara were negative for all 3 rickettsioses. Generally tick typhus was most prevalent. In certain localities, there were relatively high prevalence of murine typhus.

Single infections occurred only in about 40% of cases (Table 2). Mixed infections of tick and murine typhus were the most common.

Table 2. Proportion of single and mixed typhus infections in febrile patients.

Infections[a]	No. positive (% of total)
ST	56 (22)
TT	37 (14)
MT	11 (4)
ST, TT	40 (16)
ST, MT	7 (3)
TT, MT	77 (30)
ST, TT, MT	30 (12)

[a] ST = Scrub typhus, TT = Tick typhus, MT = Murine typhus

Overall, the majority of cases examined were Malays (50%), followed by Ibans (19%) and Indians (16%). Prevalence data based on IgG titres indicated that discounting the single Melanau and Kadazan, the Orang Asli followed by the Murut, had the highest past infection rates for scrub typhus (Table 3). The highest percent of infection with tick typhus was also found in the Orang Asli followed by the Murut, Chinese and the Iban. Murine typhus affected the Malay and Indian populations most.

The highest percent of recent infection (based on IgM titres) for scrub typhus, were in Indians followed by the Muruts (Table 4). For tick typhus, the Indians followed by the Muruts and Ibans had the highest infection rates. The Indians again had the highest infection rate for murine typhus. Generally there is no significant association ($p>0.05$) between prevalence and ethnicity.

The age disrribution of cases examined is shown in Table 5. Only 2% of cases were over 60 years old and this age group had the highest prevalence for scrub and murine typhus. Among the other age groups, those in the 21-30 years group had the highest prevalences for all 3 infections. Generally , there was no significant association ($p>0.05$) between prevalence and age.

Males formed approximately two thirds of the total number of cases seen (Table 6). There was a higher percent of females infected with scrub typhus but nor with tick and murine typhus. However, no significant association ($p>0.05$) was detected between sex and preva-

Table 3. Prevalence (based on IgG titres) of typhus infections among febrile patients of various ethnicity.

Ethnicity	No. (% of total)	Mean % +ve (2 SD)		
		Scrub typhus	Tick typhus	Murine typhus
Malay	304 (50)	17 (33)	34 (47)	29 (52)
Iban	115 (19)	26	46	17
Indian	99 (16)	27 (75)	41 (64)	29 (56)
Murut	39 (6)	67	46	18
Orang Asli	15 (2)	69 (55)	58 (76)	17 (58)
Chinese	10 (2)	42 (100)	46 (83)	0
Melanau	1 (<1)	0	100	0
Kadazan	1 (<1)	100	100	0
Others	23 (4)	54 (32)	42 (39)	23 (41)
Total	607[a]			

[a] Ethnicity of 2 patients not available

Table 4. Prevalence (based on IgM titres) of typhus infections among febrile patients of various ethnicity.

Ethnicity	No. (% of total)	Mean % +ve (2 SD)		
		Scrub typhus	Tick typhus	Murine typhus
Malay	304 (50)	10 (7)	28 (53)	17 (49)
Iban	115 (19)	7	32	15
Indian	99 (16)	19 (14)	44 (60)	26 (53)
Murut	39 (6)	13	33	10
Orang Asli	15 (2)	0 (0)	25 (50)	8 (29)
Chinese	10 (2)	8 (33)	6 (25)	0
Melanau	1 (<1)	0	100	100
Kadazan	1 (<1)	0	100	100
Others	23 (4)	11 (21)	51 (17)	18 (41)
Total	607[a]			

[a] Ethnicity of 2 patients not available

Table 5. Age distribution of febrile patients examined for typhus infections.

Age group (yrs)	No. of patients (% of total)	No. Scrub typhus +ve (%)[a]	No. Tick typhus +ve (%)[a]	No. Murine typhus +ve (%)[a]
0-10	8 (1)	0 (0)	1 (13)	0 (0)
11-20	154 (25)	6 (4)	37 (24)	18 (12)
21-30	129 (21)	15 (12)	49 (38)	31 (24)
31-40	134 (22)	10 (7)	42 (31)	25 (19)
41-50	126 (21)	14 (11)	30 (24)	15 (12)
51-60	44 (7)	3 (7)	7 (16)	4 (9)
>60	14 (2)	2 (21)	3 (21)	4 (29)
Total	609			

[a] % based on total cases in each age group

lence of the typhus infections in all the localities.

Occupation of the cases were broadly classified as agriculture-related, non-agriculture-related, housewives, students, or unemployed. There was a similar proportion of toral cases in both agriculture-based and non-agriculture-based occupations (Table 7). There was no significant association (p>0.05) between occupation and prevalences in all rhe localities.

The symptoms recorded for all and positive cases are shown in Table 8. More than 50% of the patients had headache; this symptom was also the most common among the positive cases. The other symptoms appeared in less than 10% of all cases. None of the cases had hepatomegaly or splenomegaly. No significant association was found (p>0.05) between headache and prevalence of the 3 typhus infections in all localities.

Table 6. Sex of febrile patients examined for typhus infections.

	Number (%)[a]		Total
	Female	Male	
All cases	214	393	607[b]
Scrub typhus +ve	57 (27)	75 (19)	132
Tick typhus +ve	67 (31)	132 (36)	199
Murine typhus +ve	35 (16)	88 (22)	123

[a] Percenr based on total in each sex
[b] Sex of 2 cases not identified

Discussion

Much is known about scrub typhus in Peninsular Malaysia but not in East Malaysia. Based on the present evidence of high prevalence of this infection in Selangau and Nabawan, greater research emphasis should be directed at this infection in East Malaysia.

In recent years, there has been few reports of spotted fever, to which tick typhus is grouped, occurring in the Southeasr Asia region; most of these reports are from Thailand (Sirisanthana *et al.*, 1994; Takada *et al.*, 1993). The present study clearly demonstrated thar tick typhus is present in Malaysia and has a higher prevalence than scrub typhus. This finding has some serious implications in that historically, local research and control activities have largely concentrated on scrub typhus. Due

Table 7. Occupation of febrile patients examined for typhus infections.

Occupation	Total	No. (% of total)		
		Scrub typhus	Tick typhus	Murine typhus
Agriculture-related	157	18 (11)	55 (35)	33 (21)
Non-agricultrure-related	160	19 (12)	69 (43)	44 (28)
Housewife	41	4 (100)	10 (24)	5 (12)
Student	50	4 (8)	13 (20)	5 (10)
Unemployed	13	3 (23)	7 (54)	2 (15)

Table 8. Symptoms of febrile patients examined for typhus infections.

Symptom	Total	Number (% of total)		
		Scrub typhus +ve	Tick typhus +ve	Murine typhus +ve
Headache	319	30 (9)	101 (32)	58 (18)
Pharyngitis	100	2 (2)	25 (25)	15 (15)
Abdominal pain	56	4 (7)	10 (18)	7 (13)
Vomiting	30	1 (3)	8 (27)	3 (10)
Rash	1	0 (0)	0 (0)	0 (0)
Eschar	1	1 (100)	1 (100)	1 (100)
Lymphadenopathy	9	0 (0)	1 (11)	0 (0)
Hepatomegaly	1	0 (0)	0 (0)	0 (0)
Splenomegaly	0	0	0	0

Grand total of 609 patients examined

to lack of prevalence data in the past, it is not clear whether the higher prevalence of tick typhus is a recent development or has gone undiagnosed in the past. Further studies on the natural hosts, vectors, strains of rickettsiae involved, should be conducted.

As with tick typhus, little too is known about murine typhus in Southeast Asia. It is reported to be endemic in Thailand (Sankasuwan *et al.*, 1969). Murine typhus was identified as a major cause of febrile illness in a camp for displaced Khmers in Thailand (Duffy *et al.*, 1990). More recently, a serosurvey in suburban Bangkok had also revealed the presence of murine typhus (Strickman *et al.*, 1994). The approximately 20% prevalence of murine typhus among febrile cases detected in this study, strongly indicates that this infection too merits further investigations.

The 60% of cases which tested positive to more than 1 rickettsial infection can be due to either co-infection or cross-reacting antigens. According to Tamura *et al.* (1995), the protein composition of *R. tsutsugamushi* is very different from that of the other rickettsiae. As such it is likely that cases positive to scrub typhus and one or more of the other rickettsiae, is a case of co-infection. Phylogenetic analysis of the 16S rDNA sequences also indicated that both *R. typhi* and T118 strains of tick typhus are more closely related with each other than to *R. tsutsugamushi* (Roux and Raoult, 1995). On the other hand, a broad antigenic relationship was reported between rickettsiae of the typhus and spotted fever groups (Ormsbee *et al.*, 1978). This perhaps is the reason why it was common in this study to find cases positive for both tick and murine typhus.

Other than headache, none of the other symptoms appeared to be common in the patients examined. It is uncertain whether their absence was due to the immunity level of the local population or that they were overlooked by the attending physicians. Among American troops serving in scrub typhus endemic areas, other than fever and headache which was present in all cases, lymphadenopathy was also present in 90% of the cases (Sayen *et al.*, 1946). The other symptoms were also reported in 13-46% of cases of American troops examined in Vietnam (Berman and Kundin, 1973). The predominant clinical manifestation of scrub typhus among Chinese soldiers on the Pescadores Islands of Taiwan were eschar, fever, headache, chills and lymphadenopathy (Bourgeois *et al.*, 1977). In the present study, only 1 case presented with an eschar. It has been reported that the presence of eschar in Asians is usually low (Brown *et al.*, 1976). That had been variously attributed to partial immunity and obscurement by skin colouration.

Much less is known about the symptoms common for tick and murine typhus in this region. The first cases of spotted fever group rickettsiosis in Thailand, presented with fever, headache, lymphadenopathy and petechial maculopapular rash (Sirisanthana *et al.*, 1994). Duffy *et al.* (1990) reported that in Thailand, signs and symptoms could not distinguish confirmed murine typhus from other undiagnosed illnesses. Brown *et al.* (1988) found murine typhus to be characterized by persistent fever, retro-orbital headache, and myalgias.

Scrub, tick and the rural form of murine typhus, has most often been thought to be associated with agriculture-related occupations. This may be true in semi-urban or urban localities where a sizeable proportion of the population is not in frequent contact with ecologies supportive of the rickettsial infections. As described earlier, localities were selected for this study based on their proximity to those habitats which support the natural hosts and vectors of the rickettsioses. All cases thus irrespective of their occupations, are in a way living in and surrounded by typhus favouring ecologies.

This study has reinforced in a way, how little is known about arthropod-borne rickettsioses in Malaysia and in the region. Even though morbidities and mortalities due to these rickettsioses is low in the local population because of effectiveness of most commonly used antibiotics, it is still useful to elucidate the natural pathogen-host-vector relationships so that in the eventuality that such rickettsioses become a major health problem, baseline information is available for development of effective control measures.

Acknowledgments

We are grateful to the Director, Institute for Medical Research, Kuala Lumpur, Malaysia, for permission to publish this report. The success of this study in no small way, is due to the help and collaboration rendered by the Department of Vector-borne Diseases (Ministry of Health), all staff in the participating health centers, VBDCP laboratories, Raub Hospital laboratory, Divisions of Acarology and Bacteriology in the Institute for Medical Research. This study was partially funded by a MPKSN grant no. 3-08-01-100.

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Received 29 August 1996; revised 27 December 1996; accepted for publication 28 December 1996.