

# **Acute undifferentiated fevers:**

**Khachornsakdi Silpapojakul MD**

**Prince of Songkla University**

**Hat yai, Songkla, Thailand**

# CASE 1

**Male, 45 yr. old, Dean of a medical school.**

**Hx: Had fever for 4 days, myalgia, headache**

**Traveled to Rayong 1 mo ago.**

**PE: T 39.7°C P 90/min otherwise = NAD**

**Lab: Hct 41 % , WBC 4,500 P 60 % L 25 %;**

**UA= normal**

**Malarial smears & blood cultures = negative**

**Rx: Co - trimoxazole, not improved**

# CASE 1

	OX-K	OX-2	OX-19	IIP ( <i>R. typhi</i> )
8/10/87	1:20	<1:20	1:20	1:400
18/10/87	1:20	1:40	>1:2,560	ND

Rx: 200 mg. Doxycycline p.o.  afebrile in 24 hr.

## Case 2

**28 yrs. old man, rubber-planter from Songkla**

**First admission: Dec. 1983**

**CC. : Had fever for 5 days.**

**Hx : Fever with nausea and headache, 5 days**

**Blood exam. for malaria = neg.**

**PE: T 40.5°C, P 100/min., R 26/min, BP 100/50**

**not pale nor icteric**

**Liver & Spleen not enlarged.**

**LAB: Hct 41% WBC 4,900 P 68%, L 31%, M 1%**

**Malaria = negative x 4.**

**Urinalysis = WNL**

14/12/83

21/12/83

IFA

1:5120

$\geq$ 1:5120

*(O. tsutsugamushi)*

**Course : Rx with tetracycline, defervesed within  
24 hrs.**


**Second admission (2 mos. later )**

**CC : Had fever for 3 days with chill & headache**

**PE : T 38°C, pale, not icteric,  
liver and spleen not enlarged**

**LAB: Hb 5.6 gm% WBC 8,100 P 66% L 34%**

**Thin film smear: + for *P. falciparum***

**Course: Rx with quinine and tetracycline   
defervesed in 2 days.**

# Malarial Smear

## 2005 Annual Report,

### Malaria Division, Thai CDC

<b>Year</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>
<b>No. of smears done</b>	<b>3,339,072</b>	<b>3,069,490</b>	<b>2,524,788</b>
<b>No. of positive smears</b>	<b>37,911</b>	<b>20,264</b>	<b>27,381</b>
<b>Positive rate</b>	<b>1.14%</b>	<b>0.98%</b>	<b>1.08%</b>



Scrub Typhus Infection and Related Factors Among Patients at Malarial Clinics in 3 Thai-Myanmar Border Provinces. Kaewburong K. 1995 Thesis, Mahidol University. Bangkok

**Sites: Ratchaburi, Petchaburi, Kanchanaburi**

**200 patients visiting 6 malarial clinics.**

**43 (21.5%) had malaria.**

**17 (8.5%) had serologic evidence of recent scrub typhus infection.**

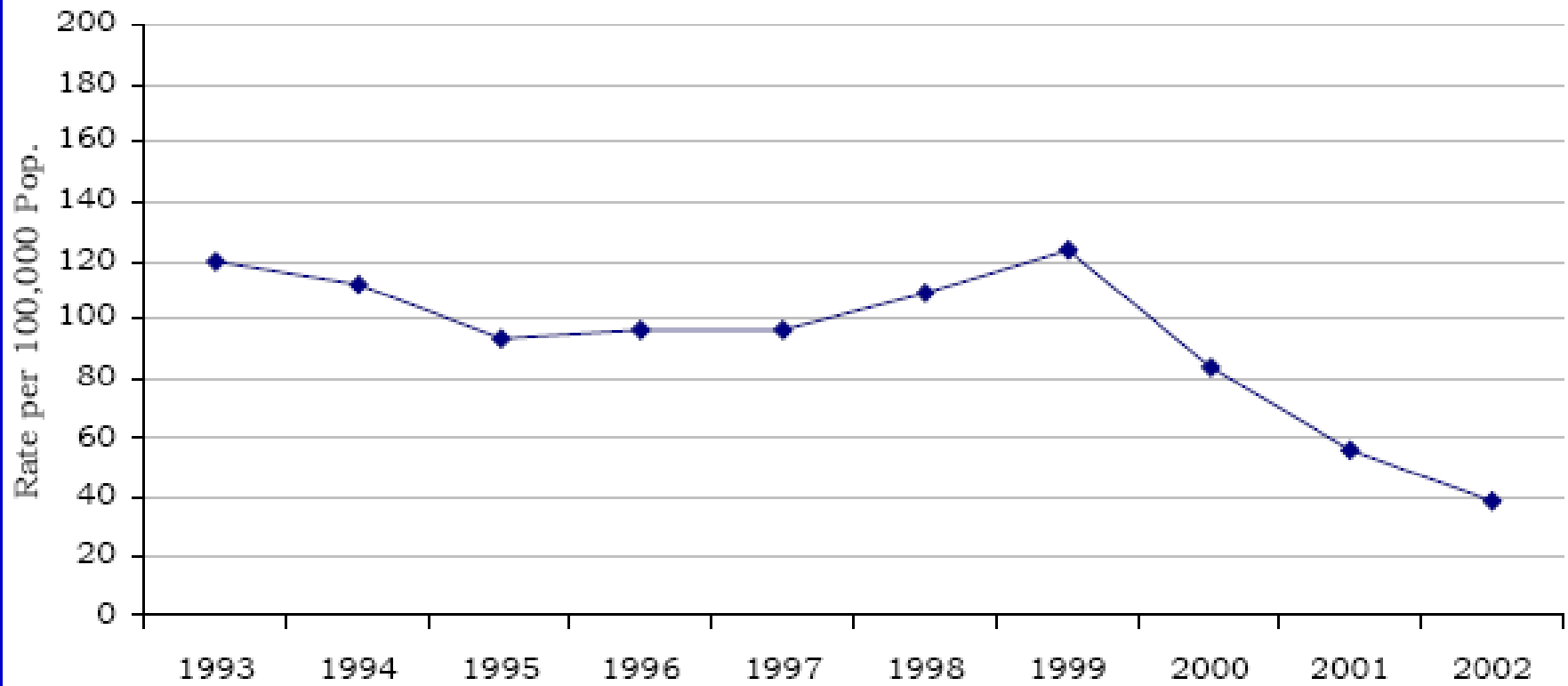
**4 (2%) had coinfection of malaria and scrub typhus.**

**In Thailand, except in some Thai- Myanmar border provinces, most febrile patients who present to malarial clinics have other diseases rather than malaria.**

**A significant proportion of patients with malaria have other coinfections such as rickettsioses or leptospirosis.**

***Ref.: Berman SJ et al. Am J Trop Med Hyg 1973;22:796-801  
Berman SJ et al. Ann Internal Med 1973;79:26-30  
Brown GW et al. Am Trop Med Hyg 1984;33:311  
Singhsilarak T et al. Southeast Asian J Trop Med Hyg  
2006;37:1-4***

Fig. 1 Reported Cases of Malaria per 100,000 Population,  
by Year, Thailand, 1992-2002.



**Source: Division of Epidemiology, Thai CDC.**

# **Acute fevers without apparent source on clinical examination: Terms**

**“Pyrexia of unknown origin or PUO”**

***(Carley JG et al. Australasian Annals of Medicine 1955;14:95)***

***(McCrumbr FR Jr. et al. Am J Trop Med Hyg 1957;6:238-256)***

# ***(Chronic) Fever of unknown origin (FUO)***

**Was defined by Drs. Petersdorf and Beeson in 1961 as:**

- (1) temperatures of  $>38.3^{\circ}\text{C}$  ( $>101^{\circ}\text{F}$ ) on several occasions;**
- (2) a duration of fever of  $>3$  weeks;**
- (3) failure to reach a diagnosis despite 1 week of inpatient investigation.**

*Petersdorf RO, Beeson PB. Medicine (Baltimore). 1961;40:1-30.*

# Acute Pyrexia of Unknown Origin (acute PUO)

**Fever  $\geq$  100°F**

**Duration  $\geq$  4 d. with  $\geq$  2 d. in hospital**

**Negative PE & Lab**

**Ref : Berman SJ *et al* : Am J Trop Med Hyg  
1973;22:796**

# **Acute undifferentiated fevers: Magnitude of problem**

**Vietnam: “Acute, undifferentiated febrile disease is the most frequent causes of admission among (~500,000) US Army personnel in Vietnam accounting for 50% of all non surgical hospitalization.”**

**Incidence = 57.1- 87.1 cases per1000 average strength per year. Second only to venereal diseases(206.3-266.0/1000) which, however, did not need hospitalization.**

*Ref. Gilbert DN et al. Ann Intern Med 1968;662:662-678*

# Annual Epidemiological Surveillance Report, Thailand

	2002	2003	2004
<b>Ac. Diarrhea</b>	<b>1,055,393</b>	<b>966,760</b>	<b>1,161,877</b>
<b>Ac. PUO</b>	<b>242,022</b>	<b>188,743</b>	<b>184,066</b>
<b>Dengue</b>	<b>114,800</b>	<b>63,657</b>	<b>39,135</b>
<b>Malaria</b>	<b>24,100</b>	<b>19,910</b>	<b>23,656</b>

**Ref : Division of Epidemiology, MOPH**



# **Acute undifferentiated fevers: Etiologies**

# Acute PUO, Northern Australia

<b>No. of patients</b>	<b>131</b>
<b><i>O. tsutsugamushi</i> isolated</b>	<b>31 (24%)</b>
<b><i>Leptospira spp.</i> isolated</b>	<b>4</b>
<b>Q fever</b>	<b>5</b>

**Ref : Carley JG *et al.* Australasian Ann Med  
1955;14:95-99**

# Acute PUO, American Soldiers, Vietnam

<b>Total No</b>	<b>793</b>
<b>1. Unknown Cause</b>	<b>377 (47.5%)</b>
<b>2. Leptospirosis</b>	<b>159 (20.1%)</b>
<b>3. Scrub typhus</b>	<b>92 (11.6%)</b>
<b>4. Japanese encephalitis</b>	<b>54 (6.8%)</b>
<b>5. Infectious Mononucleosis</b>	<b>43 (5.4%)</b>
<b>6. Gr. B Arboviruses</b>	<b>22 (2.8%)</b>
<b>7. Coxsackie virus</b>	<b>10 (1.3%)</b>
<b>8. Dengue</b>	<b>5 (0.6%)</b>
<b>9. Murine typhus</b>	<b>4 (0.5%)</b>

*Ref : Berman SJ. et al. Epidemiology of the acute fevers of unknown origin in South Vietnam. Am J Trop Med Hyg 1973;22:196*

# **Rickettsial Infections and Fever, Vientiane, Laos**

Simaly Phongmany,\* Jean-Marc Rolain,† Rattanaphone Phetsouvanh,\* Stuart D. Blacksell,\*‡§  
Vimone Soukkhaseum,\* Bouachanh Rasachack,\* Khamphong Phiasakha,\* Surn Soukkhaseum,\*  
Khamthavi Frichithavong,\* Vang Chu,\* Valy Keolouangkhot,\*¶ Bertrand Martinez-Aussel,\*¶  
Ko Chang,\* Chirapha Darasavath,\* Oudayvone Rattanaovong,\* Siho Sisouphone,\* Mayfong Mayxay,\*#  
Sisouphane Vidamaly,\*¶ Philippe Parola,† Chanpheng Thammavong,\* Mayboun Heuangvongsy,\*  
Boukong Syhavong,\* Didier Raoult,† Nicholas J. White,\*‡§ and Paul N. Newton\*‡

***EID 2006;12:256-262***

**Year of study: 2001-2003**

**Criteria for inclusion: Adults in-patients with fever and negative malarial smears.**

# Results:

<b>Total no. of patients:</b>	<b>427 (100%)</b>
<b>Total acute rickettsioses</b>	<b>115 (26.9%)</b>
<b>1. Scrub typhus</b>	<b>63 (14.8%)</b>
<b>2. Murine typhus</b>	<b>41 (9.6%)</b>
<b>3. <i>R. helvetica</i></b>	<b>8 (1.9%)</b>
<b>4. One each of <i>Rickettsia</i> AT1, <i>R. Felis</i>, <i>R.conorii</i></b>	

# Causes of acute, undifferentiated, febrile illness in rural Thailand.

*Suttinont C et al. Ann Trop Med Parasitol. 2006 ;100:363-70*

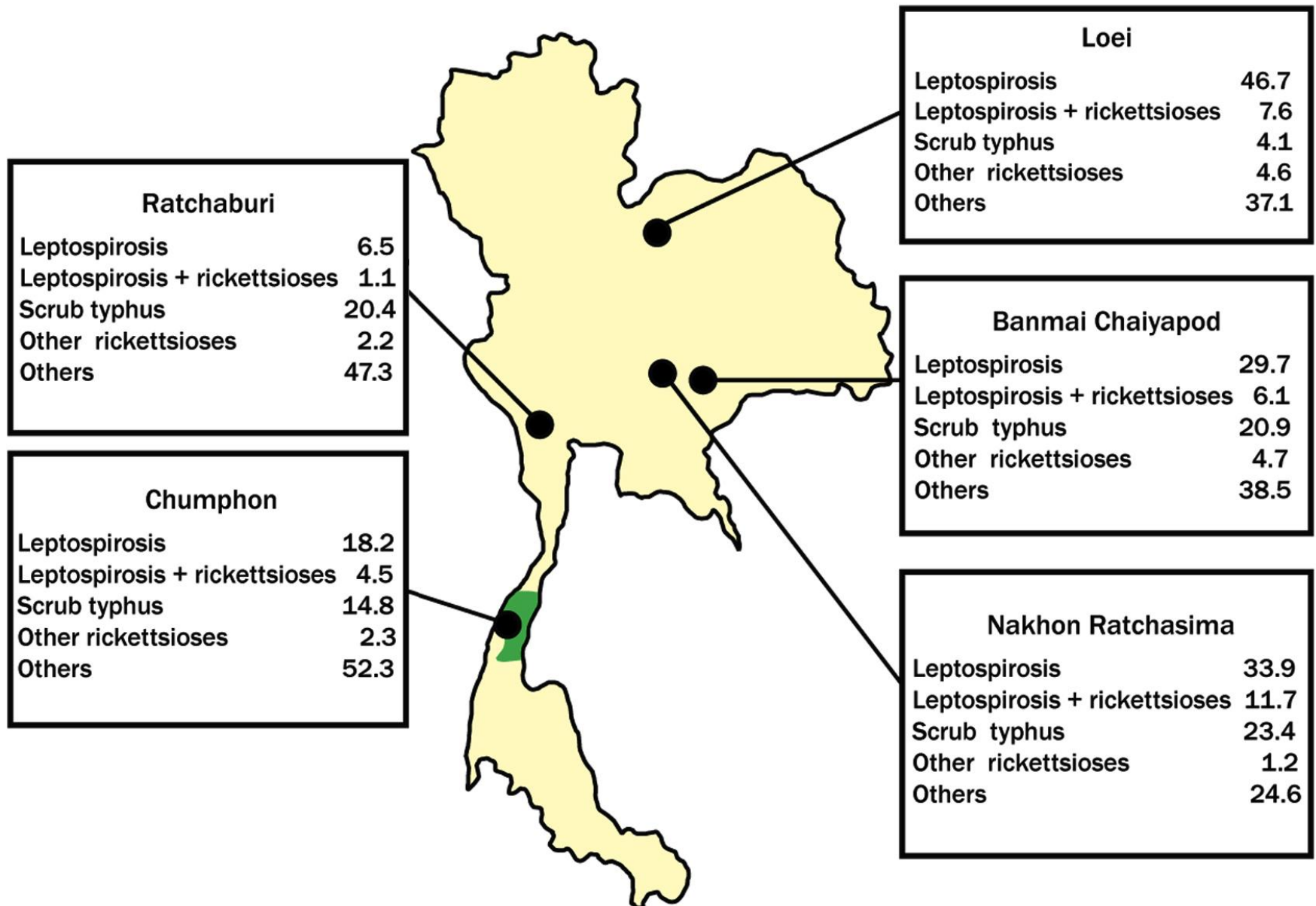
**Prospective observational study between 2001-2002**

**5 hospitals.**

**845 adults patients with fever < 15 d. and absence of an obvious focus of infection.**

# Causes of Acute Fevers at Various Study Sites

Source: Yupin Suputtamongkol



**845 patients**

**Median duration of fever, on presentation, = 3.5 days**

**Cause of their fever identified = 68.3%**

**1 Leptospirosis = 36.9%**

**2. Scrub typhus = 19.9%**

**3. Dengue infection = 10.7%**

**4. Murine typhus = 2.8%**

**5. *R. helvetica* infection = 1.3%**

**6. Q fever = 1%**



# Annual Epidemiological Surveillance Report, Thailand

	2002	2003	2004
<b>Ac. Diarrhea</b>	<b>1,055,393</b>	<b>966,760</b>	<b>1,161,877</b>
<b>Ac. PUO</b>	<b>242,022</b>	<b>188,743</b>	<b>184,066</b>
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<b>Malaria</b>	<b>24,100</b>	<b>19,910</b>	<b>23,656</b>

**Ref : Division of Epidemiology, MOPH**

# **Emerging Rickettsioses of the Thai-Myanmar Border<sup>1</sup>**

Philippe Parola,\*†‡ R. Scott Miller,\*  
Philip McDaniel,§ Sam R. Telford III,‡  
Jean-Marc Rolain,† Chansuda Wongsrichanalai,\*  
and Didier Raoult†

***EID 2003;9:592-5***

**15/ 46 patients with suspected rickettsioses  
in Sangkhlaburi between Jun 1999- Feb 2002.**

- 3 patients had scrub typhus**
- 4 patients had murine typhus**
- 8 patients had SFG rickettsioses**

1 case of ***R. felis*** : 1st case in Asia

2 cases of ***R. conorii* Indian strain** (

1 had an eschar and skin rash)

5 cases of ***R. Helvetica*** ( 3 had Hx  
of tick bite, 2 had an eschar and 1 had  
skin rash)

# Human Ehrlichiosis in Thailand

(Heppner DG et al : Lancet 1997;785-786)

- **Sangkhlaburi , Kanchanaburi**
- **50 healthy volunteers**
- **20 ( 44 % ) had *E. chafeensis* antibodies**
- **9 (18 %)  $\geq$  1 :320 IFA titers**
- **14 (28 %) had spotted fever rickettsial titers**
- **None had *E. sennetsu* antibody**

# Fever 1,629 Cases, Malaysia

Brown GW et al. Am Trop Med Hyg 1984;33:311

	Number	Percentage
<b>1. Unkown Etiology</b>	<b>515</b>	<b>31.6%</b>
<b>2. Rickettsial infections</b>	<b>327</b>	<b>20.1%</b>
<b>Scrub typhus</b>	<b>315</b>	<b>19.3%</b>
<b>3. Enteric fever</b>	<b>127</b>	<b>7.8%</b>
<b>4. Flavivirus infections</b>	<b>114</b>	<b>7.0%</b>
<b>5. Leptospirosis</b>	<b>110</b>	<b>6.8%</b>
<b>6. Malaria</b>	<b>101</b>	<b>6.2%</b>



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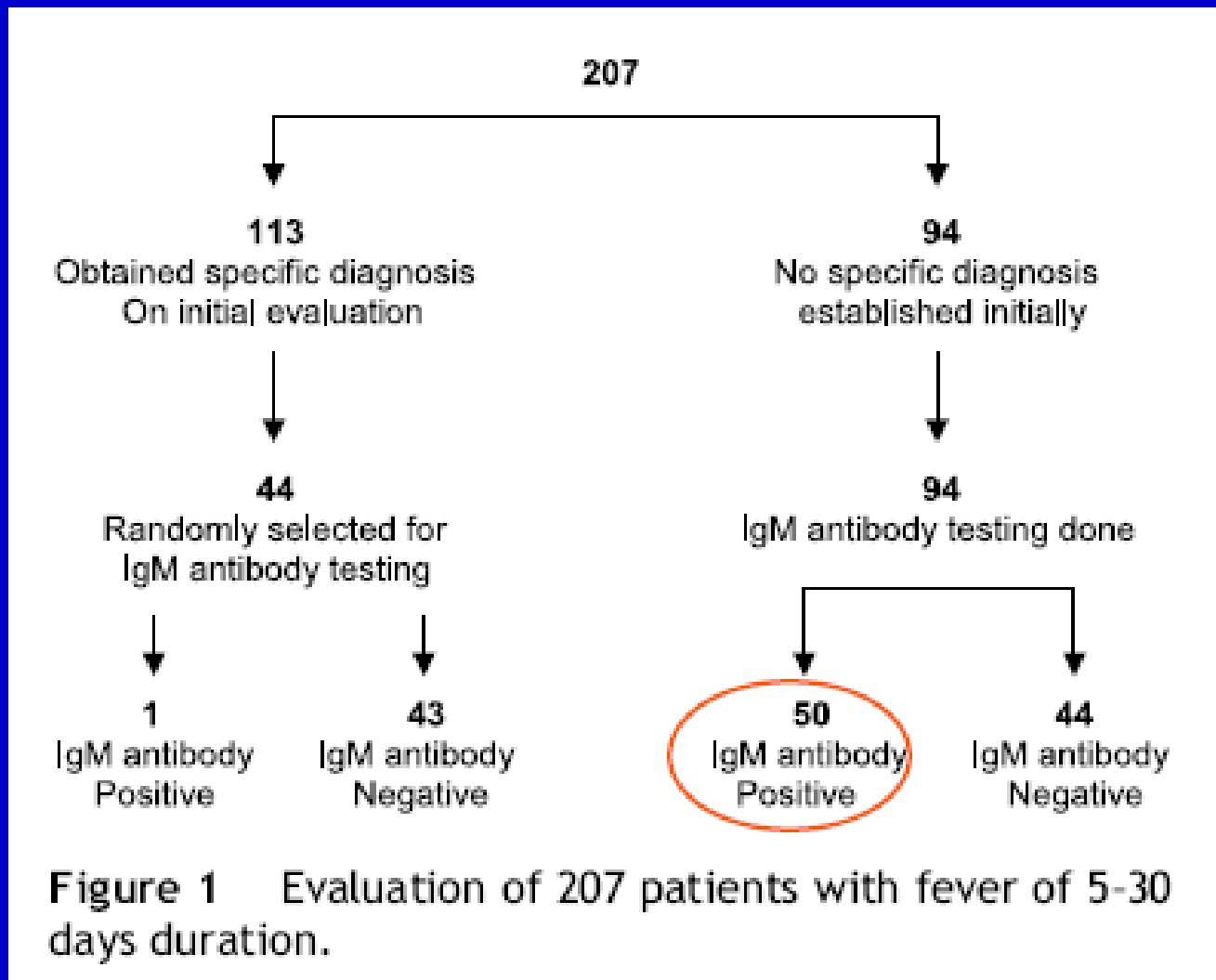
[www.elsevierhealth.com/journals/jinf](http://www.elsevierhealth.com/journals/jinf)

## Scrub typhus among hospitalised patients with febrile illness in **South India**: magnitude and clinical predictors

G.M. Varghese\*, O.C. Abraham, D. Mathai, K. Thomas, R. Aaron, M.L. Kavitha, E. Mathai

*Christian Medical College, Vellore 632004, India*

**Prospective (Oct 2002-Feb 2003) study of adult in-patients with fever of 5-30 days duration.**



**50/207(24.2%) had scrub typhus. 7/50 (14%) died.**

*Am. J. Trop. Med. Hyg.*, 70(6), 2004, pp. 670–675

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THE ETIOLOGY OF FEBRILE ILLNESS IN ADULTS PRESENTING TO PATAN  
HOSPITAL IN KATHMANDU, NEPAL

DAVID R. MURDOCH, CHRISTOPHER W. WOODS, MARK D. ZIMMERMAN, PETER M. DULL, RAM HARI BELBASE,  
ANDREW J. KEENAN, ROBERT McNAIR SCOTT, BUDDHA BASNYAT, LENNOX K. ARCHIBALD, AND  
L. BARTH RELLER

**Prospective study of all adults with fever during winter and monsoon seasons in year 2001.(Only 16% were in-patients.)**



## Results:

Murine typhus	= 97/876	= 9.9%
Paratyphoid fever*	= 57/876	= 6.5%
Typhoid fever*	= 50/876	= 5.7%
Leptospirosis	= 36/876	= 4.1%
Scrub typhus	= 28/876	= 3.2%
Malaria	= 0/876	= 0%
Dengue	= 0/876	= 0%

\* *culture- proved*

**Original Article**

Investigation of an Outbreak of Scrub Typhus in the **Himalayan Region of India**

Anuradha Sharma\*, Sanjay Mahajan<sup>1</sup>, M. L. Gupta, Anil Kanga and Vijay Sharma

**A total of 113 cases with 19 deaths (17.27 % case fatality rate) were reported in the three worst affected districts Shimla, Solan and Sirmaur in Himachal Pradesh (India) during scrub typhus outbreak in September 2003.**

# Scrub Typhus Reemergence in the Maldives

Michael D. Lewis,\* Abdul Azeez Yousuf,†  
Kriangkrai Lerdthusnee,\* Ahmed Razee,‡  
Kirkvitch Chandranoi,\* and James W. Jones\*

In summer 2002, an outbreak of febrile illness began in the Maldives in the Indian Ocean. Through April 2003, officials recorded 168 cases with 10 deaths. The Armed Forces Research Institute of Medical Sciences in Bangkok confirmed *Orientia tsutsugamushi* and conducted a joint investigation with the Ministry of Health, Maldives. These cases of scrub typhus were the first in the Maldives since World War II.

**Short Communication**

Detection of Antibodies against Spotted Fever Group *Rickettsia* (SFGR),  
Typhus Group *Rickettsia* (TGR), and *Coxiella burnetii* in  
Human Febrile Patients **in the Philippines**

Gerry Amor Camer, Marissa Alejandria<sup>1</sup>, Miguel Amor<sup>2</sup>, Hiroshi Satoh<sup>3</sup>,  
Yasukazu Muramatsu<sup>3</sup>, Hiroshi Ueno<sup>3</sup> and Chiharu Morita<sup>3\*</sup>

**157 febrile patients in the Philippines**

**2.5% were positive for *R. typhi***

**1.3% were positive for *R. japonica***

# New *Orientia tsutsugamushi* Strain from Scrub Typhus in Australia

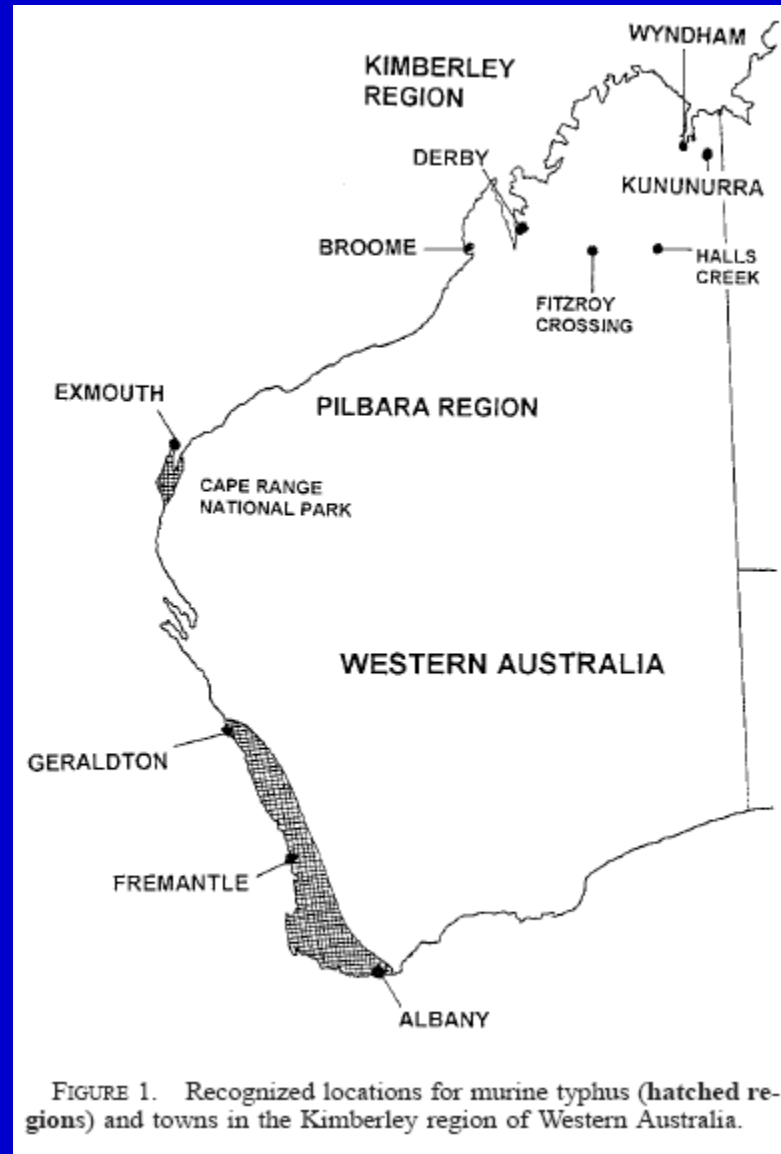
***EID 1998;4:641-4***

Dimitri M. Odorico,\* Stephen R. Graves,† Sharon Ellis,‡  
Julian Catmull,\* Zoltan Nack,† Ling Wang,† and David J. Miller\*

\*James Cook University, Townsville, Queensland, Australia; †The Geelong Hospital, Geelong, Victoria, Australia; and ‡Royal Darwin Hospital, Casuarina, Northern Territory, Australia



# Murine typhus (hatched region), Australia



## SCRUB TYPHUS IN JAPAN: EPIDEMIOLOGY AND CLINICAL FEATURES OF CASES REPORTED IN 1998

MOTOHIKO OGAWA, TOSHIKATSU HAGIWARA, TOSHIO KISHIMOTO, SADASHI SHIGA, YOSHIYA YOSHIDA, YUMIKO FURUYA, IKUO KAIHO, TADAHIKO ITO, HARUYASU NEMOTO, NORISHIGE YAMAMOTO, AND KUNIIHIKO MASUKAWA

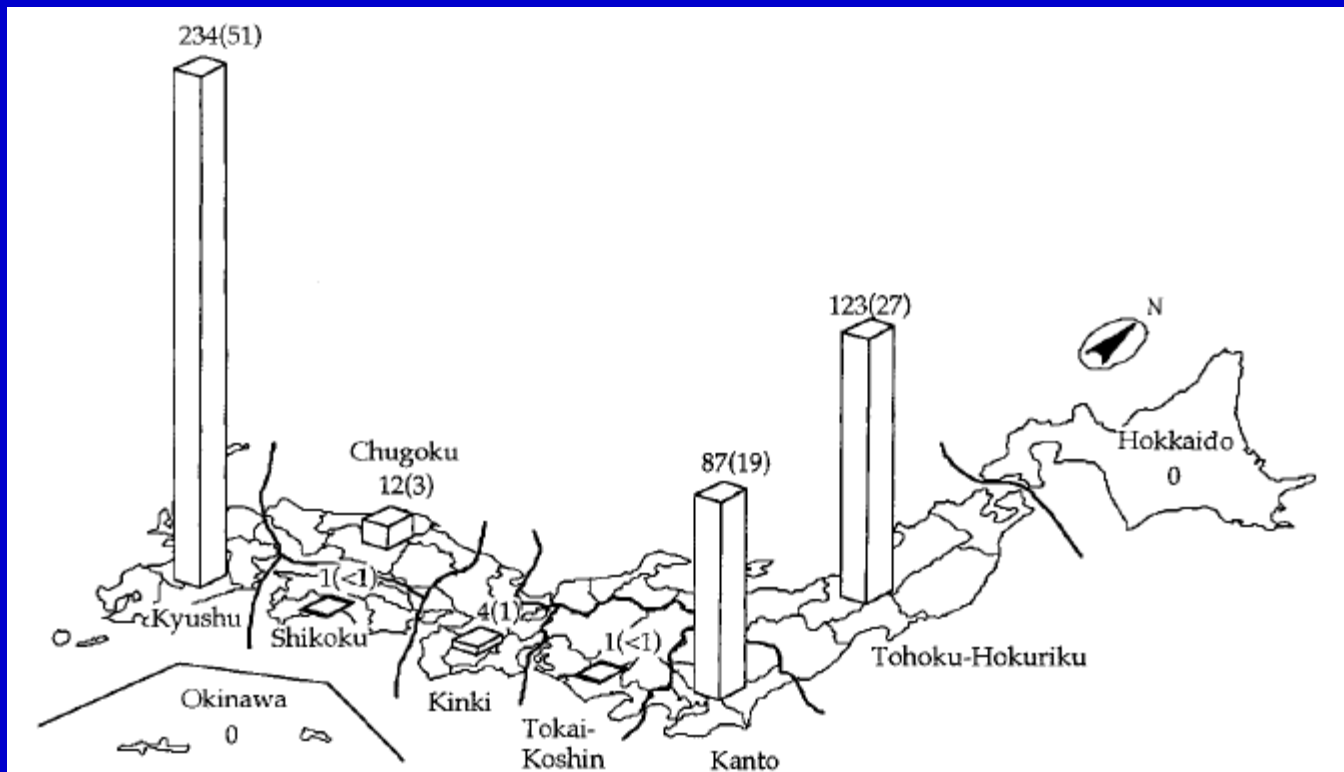
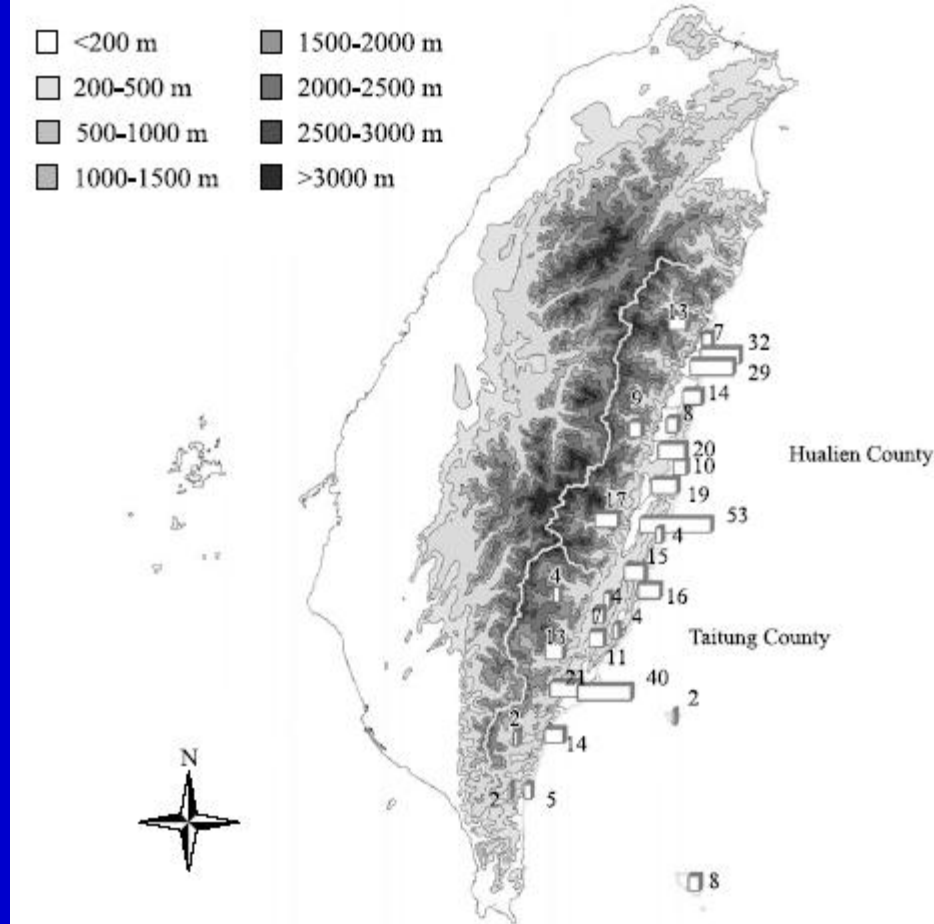


FIGURE 1. Distribution of cases of scrub typhus in Japan in 1998. A total of 462 cases of scrub typhus were reported. The number of cases (%) in each area is shown above each bar.



Jpn. J. Infect. Dis., 59, 235-238, 2006

## Original Article

# Epidemiology of Scrub Typhus in Eastern Taiwan, 2000 - 2004

Yeong-Sheng Lee, Pei-Hua Wang<sup>1</sup>, Shu-Jen Tseng, Ching-Fen Ko and Hwa-Jen Teng<sup>2\*</sup>



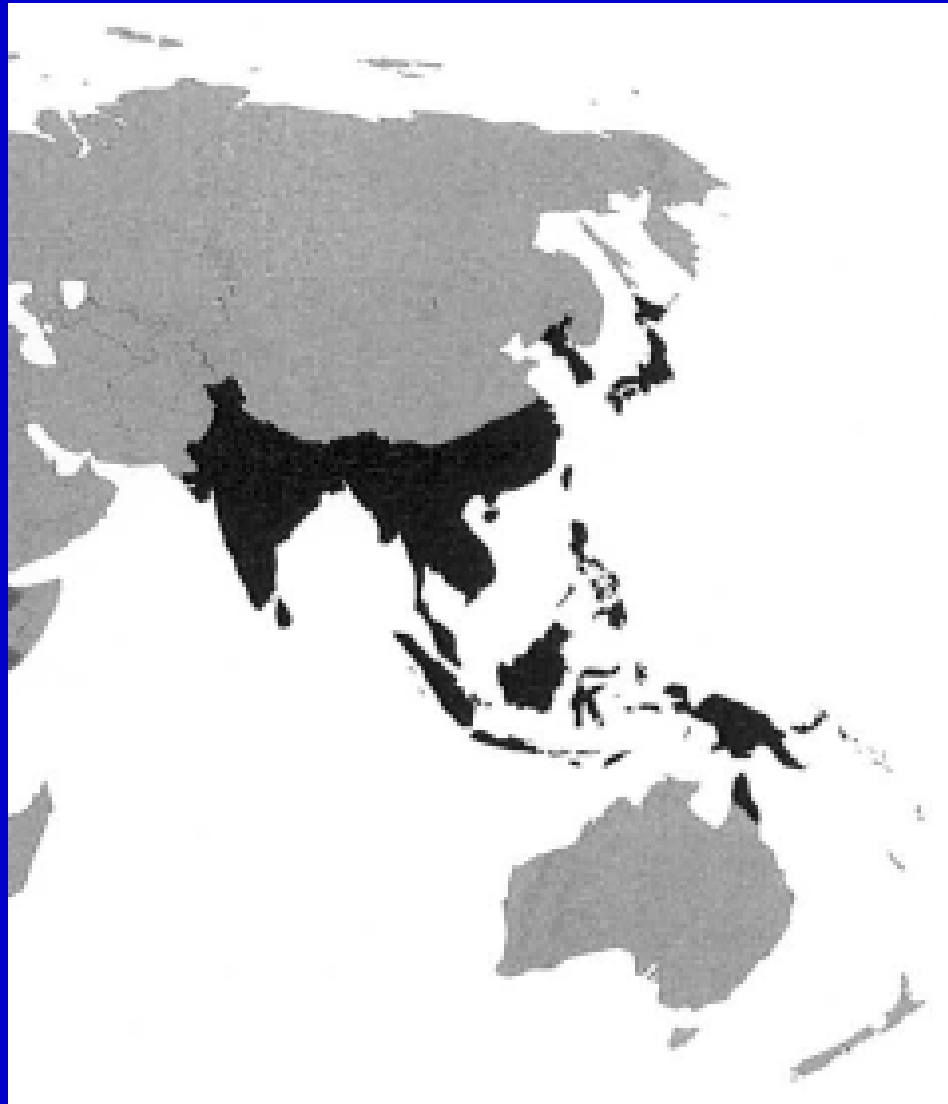
# Rickettsioses and Acute Fevers: Korea

**Table 1. Seropositive rate of 1,773 serum specimens from acute febrile patients against *Leptospira*, *Rickettsia* and Hantaan virus in 1987\***

Antigen	Positive	
	No.	(%)
<i>Leptospira</i>	219	(12.3)
<i>R. tsutsugamushi</i>	487	(27.5)
<i>R. typhi</i>	241	(13.6)
Hantaan virus	160	( 9.0)

\*Modified from Chang *et al.* (1988b).

**Ref.: Chang WH *et al.* Kor J Infect Dis 1988;20:179-186**



**Scrub Typhus Map**

# **Reemerging Murine Typhus, Japan**

**Satoshi Sakaguchi,\* Ichiki Sato,†  
Hiroaki Muguruma,\*  
Hiroaki Kawano,\*  
Yoshito Kusuhara,\* Seiji Yano,\*  
Saburo Sone,\*  
and Tsuneo Uchiyama\***

***EID 2004;10:964***

**“Murine typhus has never been reported in Japan after the 1950s, except for the three suspected cases and this case.”**

# Reemerging Murine Typhus, Hawaii 2002



**MMWR**<sup>TM</sup>

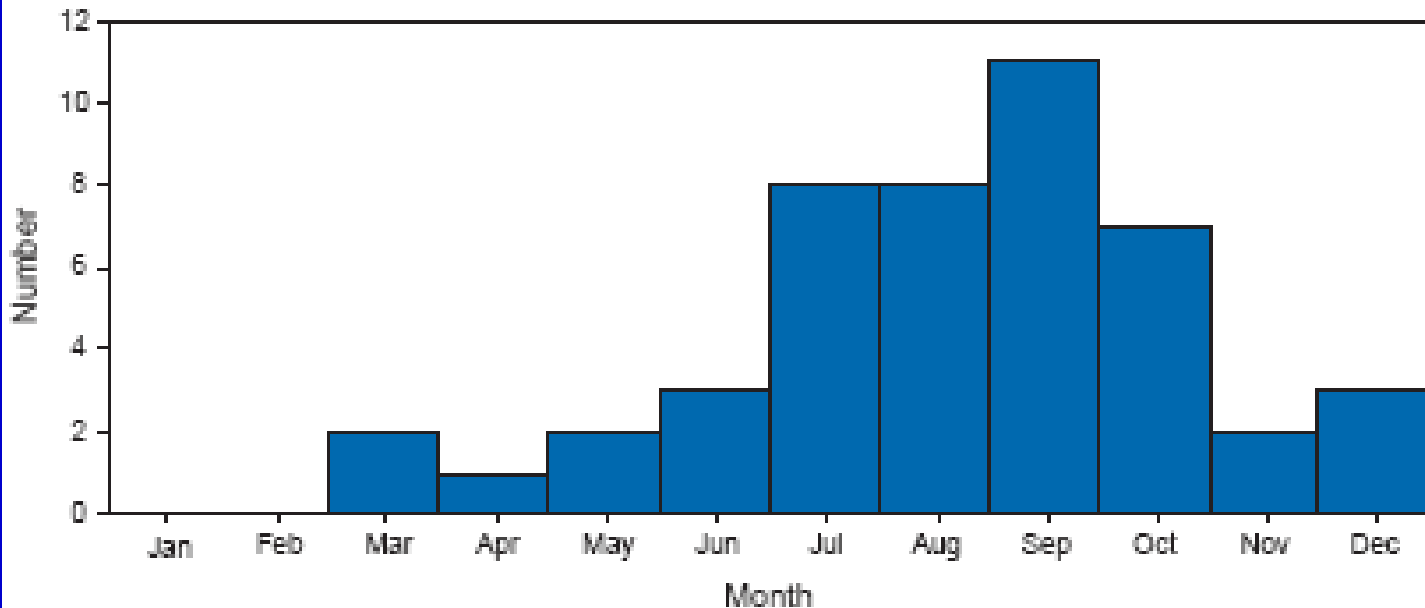


**Morbidity and Mortality Weekly Report**

Weekly

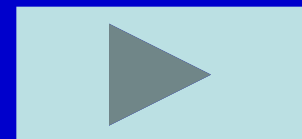
December 19, 2003 / Vol. 52 / No. 50

**FIGURE. Number\* of murine typhus cases, by month of illness onset — Hawaii, 2002**



**During 2002, a total of 47 cases of murine typhus were identified in Hawaii, the largest number recorded annually since 1947.**

**Moderate-to-severe disease was observed**  
**Acute renal failure (two cases),**  
**Gastrointestinal bleeding (two),**  
**Meningitis (two), encephalitis (one),**  
**Pneumonitis (one),**  
**Congestive heart failure with pleural effusion**  
**(one).**



# Scrub Typhus

Etiologic organism = *Orientia tsutsugamushi*

Vectors = (Mite) Chiggers



## Scrub Typhus Foci





**Scrub typhus foci**

Family Muridae  
*Bandicota bengalensis*  
E. J. Taylor  
ASMI - MHL



**Bandicoot rat**



**(Mite) Chigger ( *Leptothonnibidium* spp.)**



**Mite Chigger:Size**



**Mite Chigger: Size**

# Murine Typhus

Etiologic agent = *Rickettsia typhi*

= *Rickettsia felis* (a spotted fever group rickettsia) causing murine typhus-like fever.

Vectors = Rat Fleas (eg. *Xenopsylla cheopis*)

= Cat Fleas (eg. *Ctenocephalides felis*)

**Prevalence of *R. Typhi* vs. *R felis* in acute undifferentiated fevers in the tropics.**

**Laos: 41/427(9.6%) vs. 1/427(0.2%)**

***Phongmany S et al. EID 2006;12:256-262***

**Thailand-Myanmar border: 4/46 vs 1/46**

***Parola P et al. EID 2003;9:592-5***



***Rattus exulans***





**Oriental Rat flea: *Xenopsylla cheopis***

# Incubation Period

**Scrub Typhus: 6-21d.**

*Sayen JJ et al: Medicine 1946;25:155*

**Murine Typhus: 4-15 d.**

*Stuart BM, Pullen RL : Ann Intern Med 1942; 23:520*

**Acute undifferentiated fevers : Duration of untreated fever.**

**1. Scrub typhus : 5-36 days**

***Sayen JJ et al: Medicine 1946;25:155***

**Scrub typhus was labelled as “ Twenty days Fever” in Japan. *Tamiya T. 1962.p 24***

**2. Murine typhus : 12 - 25 days**

***Stuart BM, Pullen RL : Ann Intern Med 1942; 23:520***

**3. Leptospirosis : 4-13 days**

***McCrumbr FR Jr. et al. Am J Trop Med Hyg 1957;6:238-256***

# Problems in the diagnosis of etiologies of acute undifferentiated fevers in the tropics:

Similar signs and symptoms in Scrub and Murine typhus diseases, Leptospirosis, Typhoid and Flaviviruses infections.

- Ref.:*
- 1. Edwards GA, Dooks BM : Medicine 1960,39,117*
  - 2. Trimble AP : Proc. Roy. Soc. Med. 1957, 50, 125*
  - 3. Deller JJ et al : Ann. Intern. Med. 1967,66,1129*
  - 4. Berman SJ . Et al : Am. J. Trop. Med. 1973;220,796*



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## Paediatric scrub typhus in Thailand: a study of 73 confirmed cases

Kamkarn Silpapojakul<sup>a</sup>, Boonyarat Varachit<sup>a</sup>,  
Khachornsakdi Silpapojakul<sup>b,\*</sup>

**73 patients (M:F =1.8:1)**

**Median age = 9 y. (only 8% < 5 y. None <1 y.)**

**86% lived in rural areas**

**Mean Hx of fever =9 d.(range,1-30)**

# Pediatric Scrub Typhus: Missed Dx

Only 55% of these patients were initially diagnosed as having scrub typhus. 10% were dx as dengue hemorrhagic fever.



# Acute Undifferentiated Fevers, Songkla, Thailand

**Hospital : Hat-Yai & Rattapum Hospitals**

**Year : Oct. 1991 - Jan. 1993**

**No. of patients = 335**

**Adults = 182**

**Children = 153**

## ACUTE PUO, SONGKLA

	Adults	Children	Total
1. Scrub typhus	21	20	41(12.2%)
2. Leptospirosis	19	6	25(7.5%)
3. Dengue infection	8	17	25(7.5%)
4. Murine typhus	12	7	19(5.7%)
5. Chikungunya	2	7	9 (2.7%)
6. J.E.V.	1	4	5(1.5%)
<b>Total known</b>			<b>124(37.0%)</b>



# Symptoms & Signs of Scrub typhus in US. Soldiers

**Table 1. Prevalence of Symptoms and Signs in 87 Cases of Scrub Typhus**

Symptoms	Prevalence	Signs	Prevalence
	%		%
Fever *	100	Adenopathy	85
Headache	100	Eschar †	46
Chills	80	Spleen	43
Cough	45	Rash	34
Myalgia	32	Conjunctivitis	29
Nausea	28	Pharyngitis	28
Sore throat	26	Liver	13
Emesis	23	Muscle tenderness	6
Diarrhea	21	Nuchal rigidity	5
Back pain	20	Abdominal tenderness	5
Abdominal pain	17	Abnormal chest	
Arthralgia	11	auscultation	3
Bone pain	1	Jaundice	1

*Ref.: Berman SJ & Kundin WD. Ann Intern Med 1973;79:26-30*

# Symptoms & Signs of Murine typhus

Table 1.—Signs and Symptoms on Presentation and Throughout Course of Murine Typhus

Sign or Symptom	Cumulative Course, No. (%)	At Presentation, No. (%)
Fever	78 (98)	77 (96)
Headache	60 (75)	36 (45)
Chills	53 (66)	34 (44)
Rash	43 (54)	14 (18)
Myalgia	37 (46)	26 (33)
Malaise	23 (29)	20 (25)
Nausea	38 (48)	26 (33)
Vomiting	32 (40)	23 (29)
Anorexia	28 (35)	16 (20)
Diarrhea	21 (26)	14 (18)
Abdominal pain	18 (23)	7 (9)
Jaundice	2 (3)	2 (3)
Cough	28 (35)	13 (16)
Arthralgia	18 (23)	7 (9)
Sore throat	8 (10)	8 (10)
Dysuria and frequency	5 (6)	3 (4)
Confusion	6 (8)	4 (5)
Seizures	3 (4)	0
Stupor	3 (4)	0
Ataxia	1 (1)	1 (1)

Ref.: Dumler SJ ,Taylor JP, Walker DH. JAMA1991;266:1385-70

# Identification of the Target Cells of *Orientia tsutsugamushi* in Human Cases of Scrub Typhus

Cecilia G. Moron, Vsevolod L. Popov, Hui-Min Feng, Douglas Wear, David H. Walker

*Mod Pathol* 2001;14(8):752–759

“...immunohistochemistry study using a rabbit polyclonal antibody raised against *O. tsutsugamushi* Karp strain in paraffin-embedded archived autopsy tissues of patients with scrub typhus who died during World War II and the Vietnam War. Rickettsiae were located in endothelial cells in all of the organs evaluated...”

# Acute Undifferentiated Fevers : Pathogenesis

The pathogenesis of many diseases causing acute undifferentiated fevers are related to vascular involvement .

*eg..: Leptospirosis:Arean VM.Am J Pathol 1962;40:393-416*

*Leptospirosis:Perreira VA et al.J Pathol 1987;151:125*

*Dengue:Lei HY et al. J Biomed Sci 2001;8: 377-388*

*Dengue: Schnittler HJ , Feldmann H. Thromb Hemost 2003;89:967*

*Malaria: Pasloke BL, Howard RJ:Annu Rev Med 1994;45:293-295*

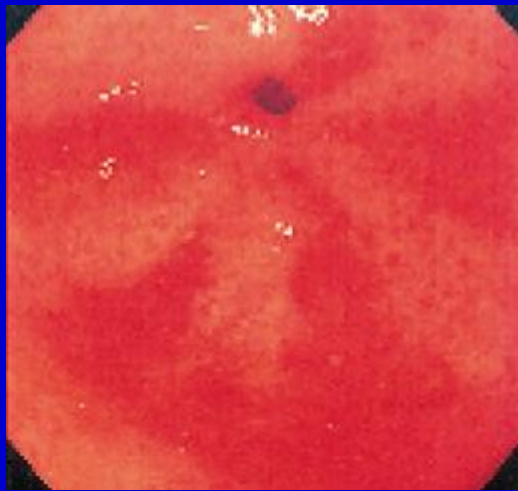
**In Thailand Typhus Disease is called “Kai-raak-saad” which literally means “Big vomiting disease”**

# The Clinical Significance of Upper Gastrointestinal Endoscopy in Gastrointestinal Vasculitis Related to Scrub Typhus

*Endoscopy 2000; 32 (12): 950– 955*

S. J. Kim<sup>1</sup>, I. K. Chung<sup>1</sup>, I. S. Chung<sup>1</sup>, D. H. Song<sup>2</sup>, S. H. Park<sup>1</sup>, H. S. Kim<sup>1</sup>, M. H. Lee<sup>1</sup>

**Endoscopy were done in 85 of 256 scrub typhus patients. Lesions of the 58 patients without Hx of NSAID Rx were:**



**Petechiae(11/58)**



**Erosions(16/58)**



**Ulcers(17/58)**

**Gastric biopsy were done in 10 patients. All showed the presence of vasculitis.**



# Acute Hearing Loss Due to Scrub Typhus: A Forgotten Complication of a Reemerging Disease

*EID 2006;42:6-8*

R. Premaratna,<sup>1</sup> T. G. A. N. Chandrasena,<sup>2</sup> A. S. Dassayake,<sup>3</sup>  
A. D. Loftis,<sup>4</sup> G. A. Dasch,<sup>4</sup> and H. J. de Silva<sup>1</sup>

Patient	Duration of fever in days	Type of hearing loss (no. of days since onset)	Clinical signs and symptoms present			
			Eschar	Pneumonitis	Myocarditis	Encephalitis
1	12	Deaf (~14)	Yes	Yes	Yes	Yes
2	11	Deaf (~10)	Yes	Yes	No	No
3	10	Deaf (~9)	Yes	Yes	No	No
4	13	Tinnitus (~11)	Yes	Yes	No	No
5	12	Tinnitus (~11)	Yes	Yes	No	No
6	14	Deaf (~9-11)	No	Yes	Yes	Yes

# A STUDY OF FEBRILE ILLNESSES ON THE THAI-MYANMAR BORDER: PREDICTIVE FACTORS OF RICKETTSIOSIS

Amy L Pickard<sup>1,2</sup>, Philip McDaniel<sup>3</sup>, R Scott Miller<sup>1</sup>, Nichapat Uthaimongkol<sup>1</sup>,  
Nillawan Buathong<sup>1</sup>, Clinton K Murray<sup>4</sup>, Sam R Telford III<sup>5</sup>, Philippe Parola<sup>1,5,6</sup>  
and Chansuda Wongsrichanalai<sup>1</sup>

<sup>1</sup>Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand; <sup>2</sup>University of

***Southeast Asian J Trop Med Publ Health 2004;35:657-663***



Commonly reported symptoms among the 15 cases and 163 controls.

Symptoms/ History	Cases		Controls		Crude OR <sup>b</sup> (95% CI <sup>c</sup> )
	N (%)	No. of days <sup>a</sup>	N (%)	No. of days <sup>a</sup>	
<u>Rash/history of arthropod bite</u>	7 (46.7)	3-60	6 (3.7)	2-14	<u>22.90 (6.23, 84.13)</u>
Shaking chills	6 (40.0)	1-14	91 (55.8)	1-30	0.53 (0.18, 1.55)
Headache	12 (80.0)	1-14	145 (89.0)	1-30	0.50 (0.13, 1.93)
Muscle pain	10 (66.7)	1-14	142 (87.1)	1-30	0.30 (0.09, 0.95)
Cough	5 (33.3)	1-12	83 (50.9)	1-240	0.48 (0.16-1.47)
Nausea	7 (46.7)	1-7	86 (52.8)	1-16	0.78 (0.27, 2.26)
Vomiting	5 (33.3)	1-3	43 (26.4)	1-7	1.40 (0.45, 4.31)
Abdominal pain	6 (40.0)	1-10	48 (29.5)	1-120	1.60 (0.54, 4.73)
Diarrhea	2 (13.3)	2-10	17 (10.4)	1-30	1.32 (0.27, 6.36)

<sup>a</sup>Number of days symptom was experienced; <sup>b</sup>OR = Odds ratio; <sup>c</sup>CI = confidence interval

Selected clinical signs of the 15 cases and 163 controls.

Signs	Cases		Controls		Crude OR (95% CI)
	N	(%)	N	(%)	
<u>Eschar</u>	6	<u>(40.0)</u>	5	<u>(3.1)</u>	<u>21.07 (5.39, 82.38)</u>
<u>Rash</u>	4	<u>(26.7)</u>	13	<u>(8.0)</u>	<u>4.20 (1.17, 15.04)</u>
Hepatomegaly	4	(26.7)	16	(9.9)	3.32 (0.95, 11.64)
Lymphadenopathy	2	(13.3)	29	(17.9)	0.71 (0.15, 3.30)
Abnormal breath sound/chest x-ray	2	(13.3)	12	(7.4)	1.94 (0.39, 9.59)
Pulmonary rales	2	(13.3)	7	(4.3)	3.43 (0.65, 18.22)

## **Emerging rickettsial infections in Sri Lanka: the pattern in the hilly Central Province**

S. A. M. Kularatne<sup>1</sup>, J. S. Edirisingha<sup>2</sup>, I. B. Gawarammana<sup>1</sup>, H. Urakami<sup>3</sup>, M. Chenchittikul<sup>4</sup> and I. Kaiho<sup>5</sup>

**118 patients with 2 or more of inclusion criteria:**

**1. Fevers > 5 d.**

**2. Skin rash**

**3. Rapid defervescence after Rx with tetracycline**

**Table 3** Types of rickettsial infections identified from first and second batches of sera and distribution of rickettsioses

Rickettsiae	Japan	Thai	Total	Acute
			<i>n</i> (%)	cases* <i>n</i> (%)
<i>Orientia tsutsugamushi</i> (OT)	11	1	12 (20)	8 (13)
Spotted fever group (SFG)	4	17	21 (35)	10 (16)
<i>Rickettsia typhi</i> (RT)	0	4	4 (7)	2 (3)

# Eschar



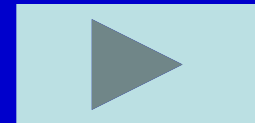
# ***Orientia tsutsugamushi* in Eschars from Scrub Typhus Patients**

Yun-Xi Liu,\* Wu-Chun Cao,\* Yuan Gao,† Jing-Lan Zhang,† Zhan-Qing Yang,† Zhong-Tang Zhao,‡  
and Janet E. Foley§

***EID 2006;12:1109-1112***

**7 eschar specimens were collected 6-15  
days after chloramphenicol Rx.**

**All were positive for *O. tsutsugamushi*  
by PCR reaction targeting the Sta56  
gene.**



# Scrub typhus : Eschar

**If presents, it signifies either scrub typhus or spotted fevers. (Murine typhus produces no eschar.)**

# Scrub typhus : Prevalences of Eschar

**46% of American patients in Vietnam**

*Ref : Ann Intern Med 1973;79:26*

**60% of 535 Americans + Chinese in Assam & Burma**

*Ref.:Medicine 1946;25:155*

**2% of 64 Malaysian in Pahang, Malaysia**

*Ref.:Trans R Soc Trop Med Hyg 1976;70:444*





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## Scrub typhus among hospitalised patients with febrile illness in **South India**: magnitude and clinical predictors

G.M. Varghese\*, O.C. Abraham, D. Mathai, K. Thomas, R. Aaron, M.L. Kavitha, E. Mathai

*Christian Medical College, Vellore 632004, India*

**Only 8% of the Indian patients had an eschar and 2% had maculo-papular rash.**

*Am. J. Trop. Med. Hyg.*, 70(6), 2004, pp. 670–675

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THE ETIOLOGY OF FEBRILE ILLNESS IN ADULTS PRESENTING TO PATAN  
HOSPITAL IN KATHMANDU, NEPAL

DAVID R. MURDOCH, CHRISTOPHER W. WOODS, MARK D. ZIMMERMAN, PETER M. DULL, RAM HARI BELBASE,  
ANDREW J. KEENAN, ROBERT McNAIR SCOTT, BUDDHA BASNYAT, LENNOX K. ARCHIBALD, AND  
L. BARTH RELLER

**None of 28 Nepalese patients with scrub typhus had an eschar.**

**Why low prevalences of eschar?**







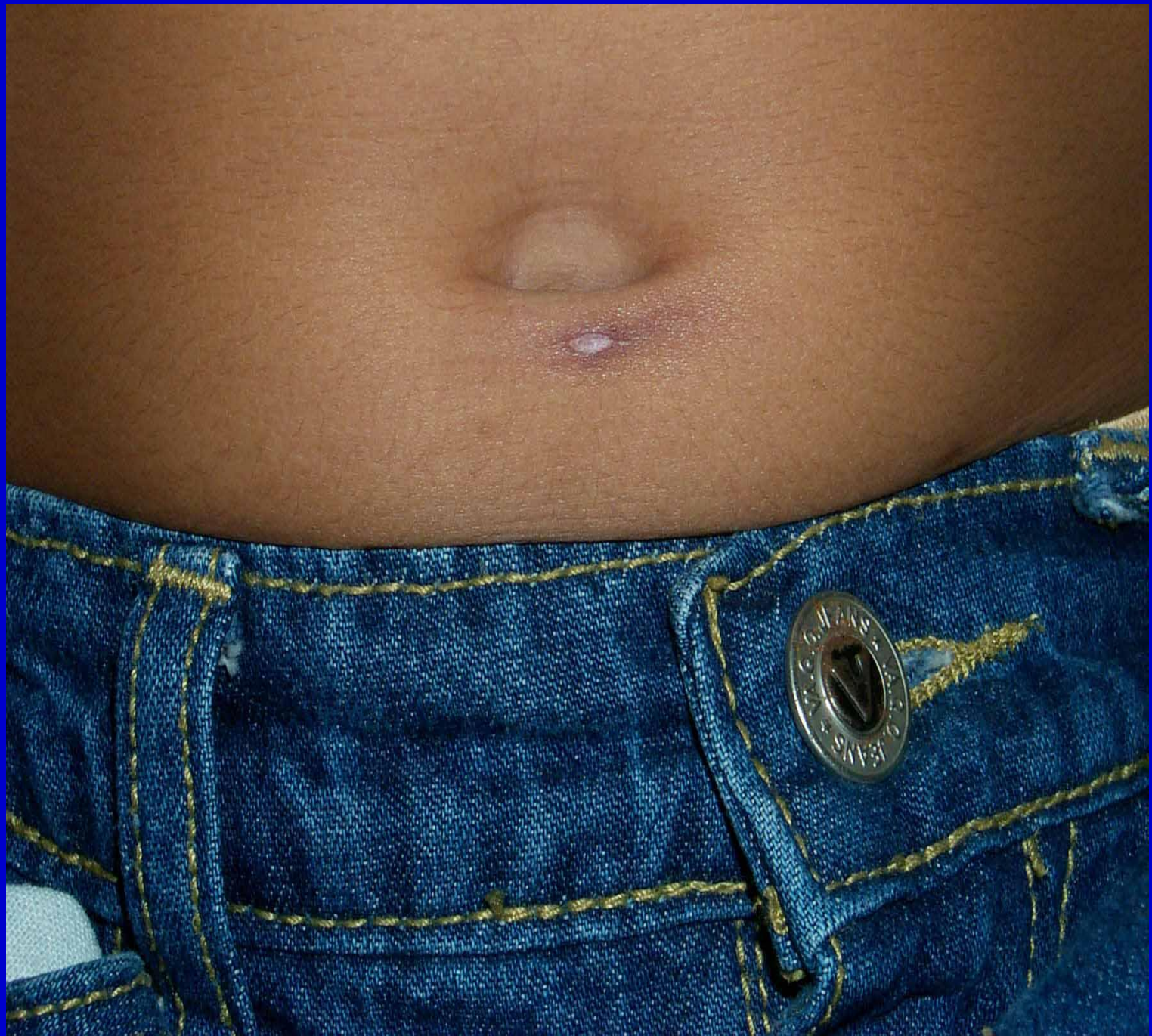
# Why low prevalences of eschar?

- 1. Because of the behaviour of the chiggers (negative geotaxis and negative phototaxis), only one-third of the bite-sites were on the sun-exposed areas.**
- 2. The eschar may not have the characteristic black scab especially in moist areas or it may lose its top if examined late in the course of disease.**











# Acute Undifferentiated Fevers: Skin Rash

---

## Scrub typhus

- 34 - 71 % in Caucasians; onset: day 3 - 8  
(Berman SJ, Kundin WE: *Ann Intern Med* 1973;79:26)  
(Sayen JJ et al: *Medicine* 1973;79:26)
- 30% in Thais; evanescent ; petechiae 4 %  
(Silpapojakul K et al: *Weekly Epidemiology Report* 1986;17:341)



# Acute Undifferentiated Fevers: Skin Rash

---

## Murine typhus

- 58 - 90 % in Caucasians; onset = day 2 - 8  
(Stuart BM, Pullen RL: *Ann Intern Med* 1945;23:520)  
(Miller ES, Beeson PB: *Medicine* 1946;25: 1)
- 20 % of 137 Thais, 4% =petechiae  
(Silpapojakul K et al. *QJM* 1993;86:43-47)



# **Acute Undifferentiated Fevers : Skin rash**

## **Leptospirosis**

**- petechial rash (Fort Bragg Fever )**

**(JAMA 1943;122:361 )**

**(Ann Intern Med 1982;96:789)**

**- 3 in 116 Thais .**

**(Silpapojakul K:Weekly Epidemiological Report 1988;19:609)**

# Acute Undifferentiated Fevers : Rash

**Typhoid:**

**0/318 adult cases**

**(Anderson KE et al : Am J Trop Med Hyg 1976;25:116 )**



# **Acute Undifferentiated Fevers:Skin Rash**

- if present, think of rickettsial diseases or dengue rather than leptospirosis, malaria or typhoid fever**
- if petechial rash; think of Dengue, Spotted Fever or Meningococemia**

# **Scrub Typhus and Murine Typhus: Laboratory Diagnosis**

# Scrub Typhus and Murine Typhus: Laboratory Diagnosis

## 1. Mouse inoculation.

*Carley, J.G. et al. Australasian Ann. Med. 1955;4:91-99.*

## 2. Serologic methods.

*Pradutkanchana, J. et al. Trans. R. Soc. Trop. Med. Hyg. 1997; 91,425-428.*

# IFA in Scrub Typhus: Sensitivity & Specificity

TABLE 3

*Indirect fluorescent antibody titers in 262 sera from scrub typhus patients (D), and in 335 from control patients (C), related to week of illness*

Reciprocal titer	Week of illness								Total	
	1		2		3		>3		D	C
	D	C	D	C	D	C	D	C	D	C
0-50	30	140	9	78	2	27	0	17	41	262
100	17	25	14	19	4	2	2	1	37	47
200	13	6	21	6	17	1	6	0	57	13
400	12	5	26	4	12	0	8	1	58	10
≥800	12	2	31	0	22	1	4	0	69	3
Total	84	178	101	107	57	31	20	19	262	335
Specificity*		0.96		0.96		0.97		0.95		0.96
Sensitivity*	0.29		0.56		0.60		0.60		0.48	

\* At ≥1:400.

**Brown GW et al. Am J Trop Med Hyg 1983;32:1101**



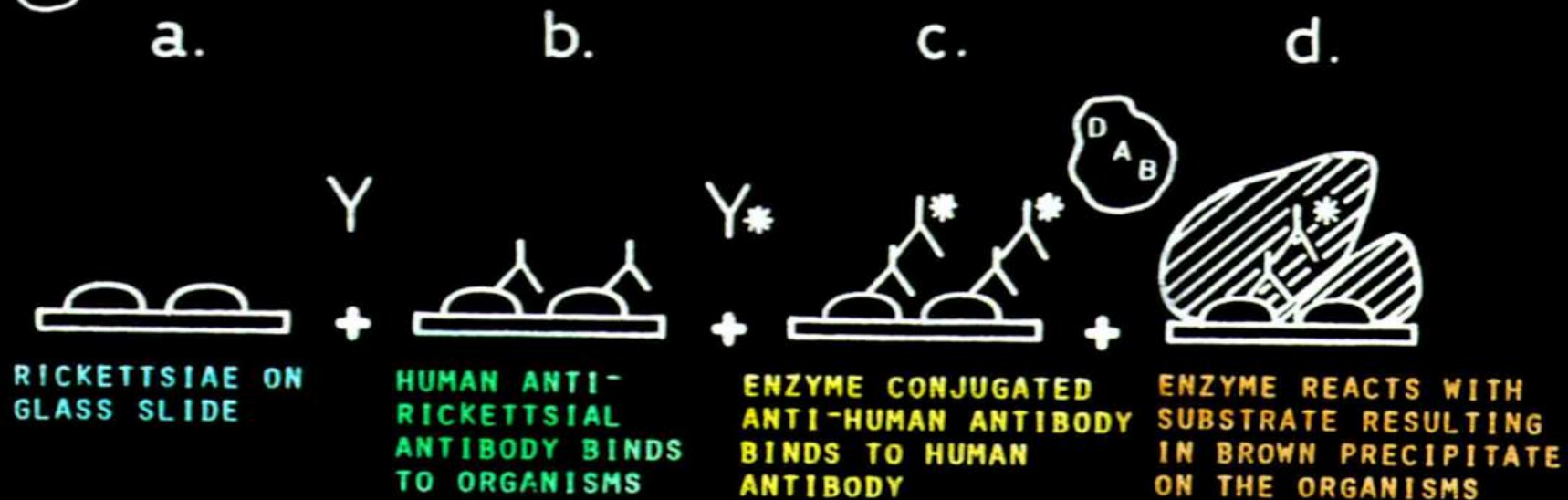
## **Comparative evaluation of four serodiagnostic tests for scrub typhus in Thailand**

---

**Jintana Pradutkanchana<sup>1</sup>, Khachornsakdi Silpapojakul<sup>2</sup>, Helene Paxton<sup>3</sup>, Sukone Pradutkanchana<sup>1</sup>, Daryl J. Kelly<sup>4,5</sup> and Daniel Strickman<sup>4</sup>** *<sup>1</sup>Departments of <sup>1</sup>Pathology and <sup>2</sup>Medicine, Faculty of Medicine, Prince of*

# Indirect Immunoperoxidase (IIP) antibody test

Fig.1





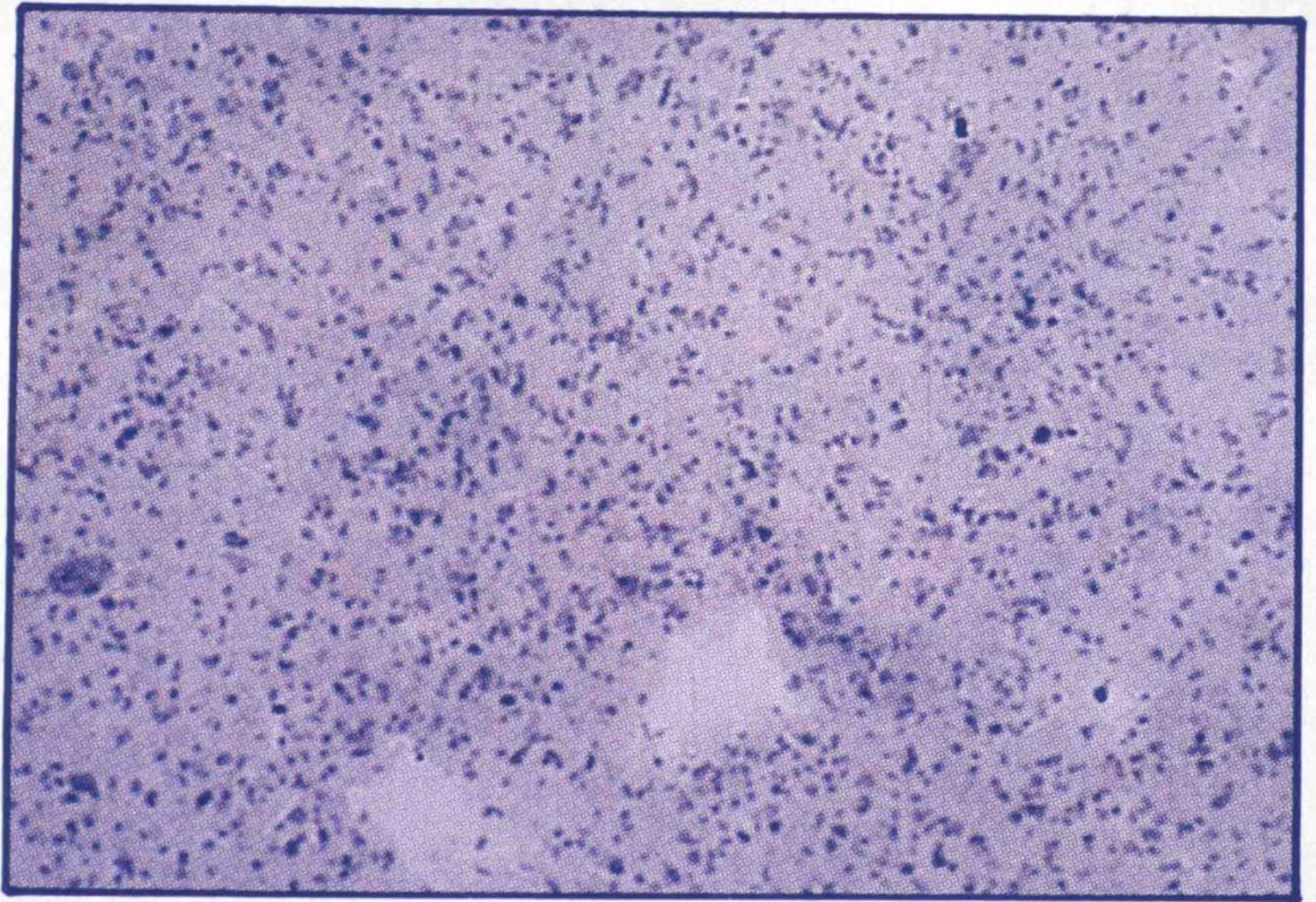


FIG. 11. Positive Stained Organisms.



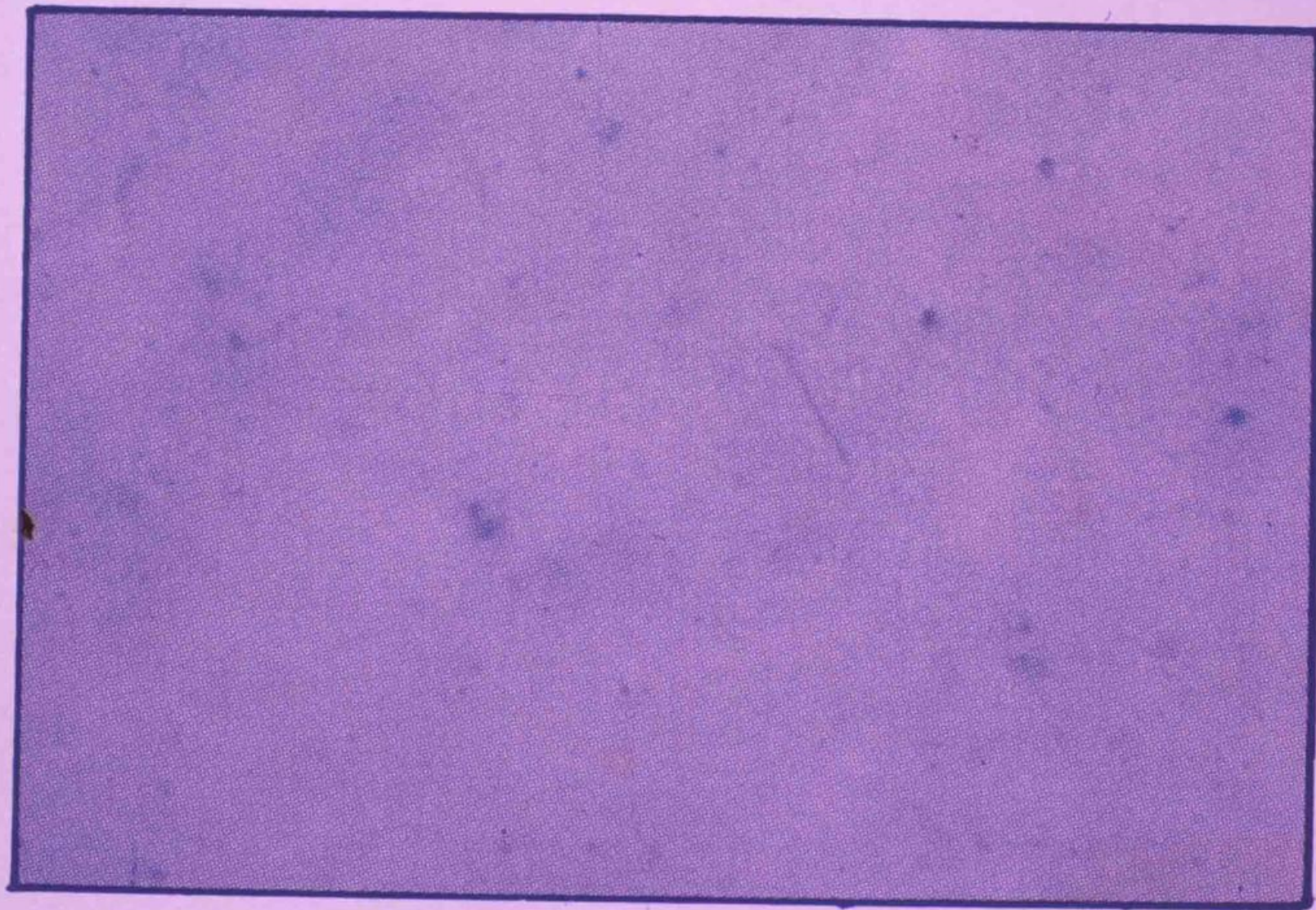


FIG. 12. Negative Stained Organisms.



# Scrub Typhus: Indirect Immunoperoxidase Test

**Table 2. Performance of the indirect immunoperoxidase test for the diagnosis of scrub typhus compared with the indirect immunofluorescence assay**

Cut-off titres	Immunoperoxidase test		Indirect immunofluorescence assay	
	Overall sensitivity (%) <sup>a</sup>	Overall specificity (%) <sup>a</sup>	Sensitivity with acute sera (%)	Sensitivity with acute sera (%) <sup>a</sup>
1:3200	27.6 (44/117)	100 (75/75)	22.2 (12/54)	18.5 (10/54)
1:1600	65.8 (77/117)	100 (75/75)	46.3 (25/54)	37.0 (20/54)
1:800	80.3 (94/117)	100 (75/75)	62.9 (34/54)	51.9 (28/54)
<b>1:400</b>	90.6 (106/117)	100 (75/75)	<b>79.6 (43/54)</b>	<b>68.5 (37/54)</b>
1:200	94.9 (111/117)	98.6 (74/75)	88.9 (48/54)	79.6 (43/54)
1:100	97.4 (114/117)	97.3 (73/75)	94.4 (51/54)	87.0 (47/54)

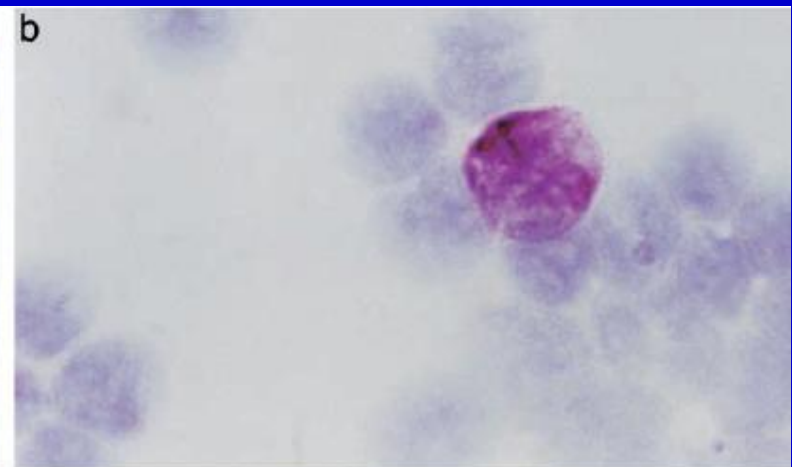
*Ref.: Pradutkanchana, J. et al. Trans. R. Soc. Trop. Med. Hyg. 1997; 91,425-428.*

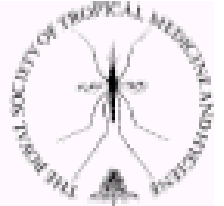
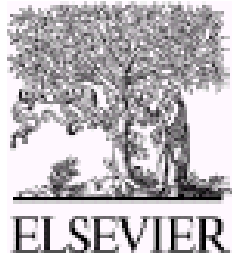
# **Rapid Diagnostic Test for Scrub Typhus**

- 1. Direct Immunofluorescent Staining.**
- 2 Immunoalkaline phosphatase Staining**
- 3. PCR**

## *ORIENTIA TSUTSUGAMUSHI* IN PERIPHERAL WHITE BLOOD CELLS OF PATIENTS WITH ACUTE SCRUB TYPHUS

DOUGLAS S. WALSH, KHIN SAW MYINT, PACHAREE KANTIPONG, KRISADA JONGSAKUL, AND GEORGE WATT





[www.elsevierhealth.com/journals/trst](http://www.elsevierhealth.com/journals/trst)

## Evaluation of nested PCR for the diagnosis of scrub typhus among patients with acute pyrexia of unknown origin

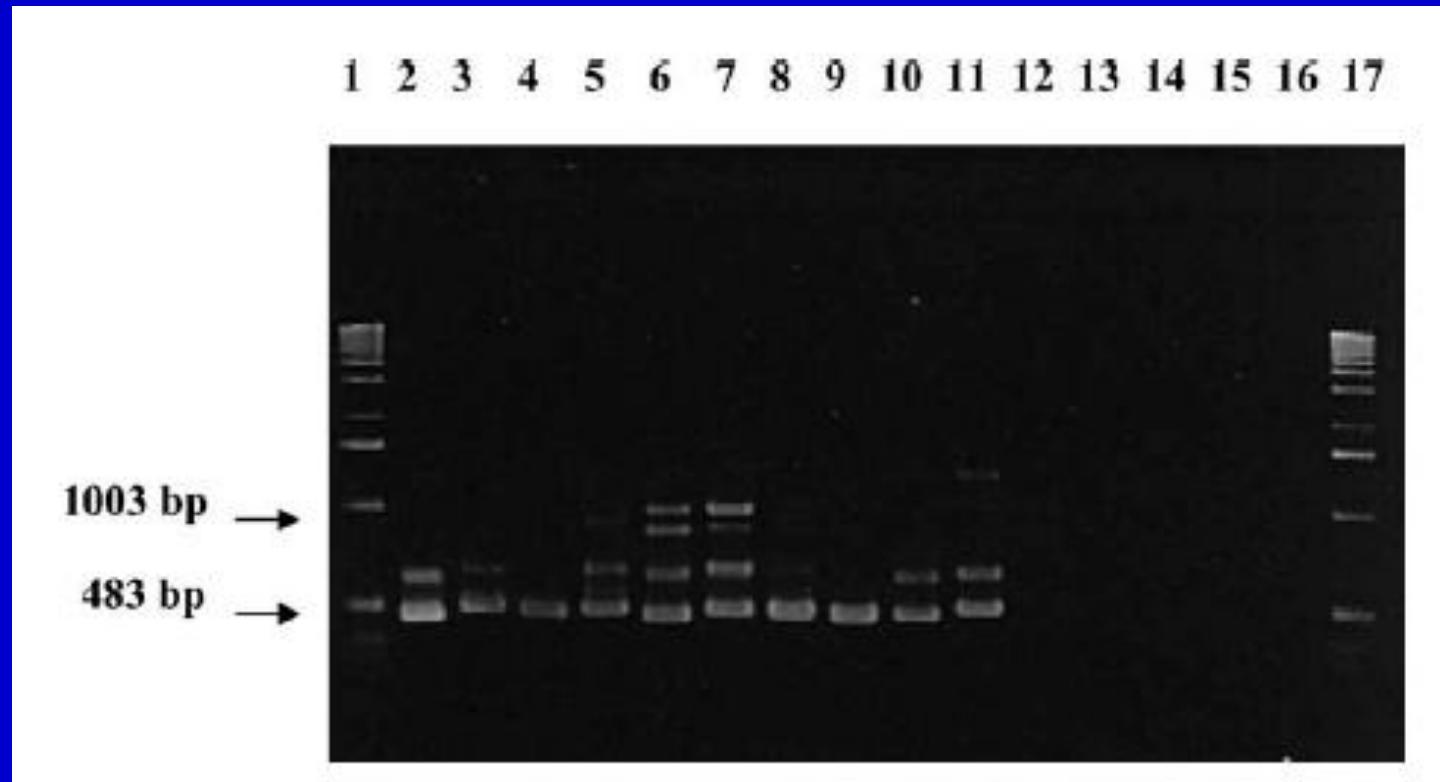
Watcharee Saisongkorh<sup>a</sup>, Mongkol Chenchittikul<sup>a</sup>,  
Khachornsakdi Silpapojakul<sup>b,\*</sup>

***PCR analysis:*** The oligonucleotide primers used were based on the nucleotide sequences of a gene encoding for the 56-kDa antigen of a Gillium strain of *O. tsutsugamushi*.

**Primers p34** (5'-TCA AGC TTA TTG CTA GTG CAA TGT CTGC-3') **and p55** (5'-AGG GAT CCC TGC TGC TGT GCT TGC TGC G-3') **were used to amplify a 1,003-bp fragment.**

then **nested primers p10** (5'-GAT CAA GCT TCC TCA GCC TAC TAT AAT GCC-3') **and p11** (5'-CTA GGG ATC CCG ACA GAT GCA CTA TTA GGC-3') **were used to amplify a 483-bp fragment.**

## *Specificity of the nested PCR assay:*



*Lanes 2—11, Orientia tsutsugamushi strains*

*Lane 12, Rickettsia typhi , Lane 13, Thai tick typhus rickettsia*

*Lane 15, Vero cells; Lane 16, distilled water.*

Patient no.	Days after onset when blood was drawn	IFA	Nested PCR
1	5	-	+
2	6	+	+
	17	+	+
3	7	-	+
	14	+	+
4	10	-	+
5	10	+	+
	18	+	-
6	11	+	+
	19	+	-
7	14	+	+
8	18	+	+
9	18	+	+
10	22	-	+
11	22	+	+
12	33	+	+

# Persistence of *O. tsutsugamushi* DNA

Days after onset when blood was drawn	Days after doxycycline treatment	IFA	Nested PCR
5	1	-	+
6	a	+	+
17	11	+	+
7	2	-	+
14	9	+	+
10	b	-	+
10	a	+	+
18	7	+	-
11	a	+	+
19	8	+	-
14	a	+	+
18	b	+	+
18	8	+	+
22	10	-	+
22	b	+	+
33	27	+	+



## Detection of *Rickettsia tsutsugamushi* in Experimentally Infected Mice by PCR

SUN-HO KEE,† IN-HAK CHOI, MYUNG-SIK CHOI, IK-SANG KIM, AND WOO-HYUN CHANG\*

*Department of Microbiology, College of Medicine, Seoul National University,  
Seoul 110-799, Republic of Korea*

# Scrub Typhus: PCR vs. Cultures

TABLE 1. Comparison of the results of various methods for detecting *R. tsutsugamushi*

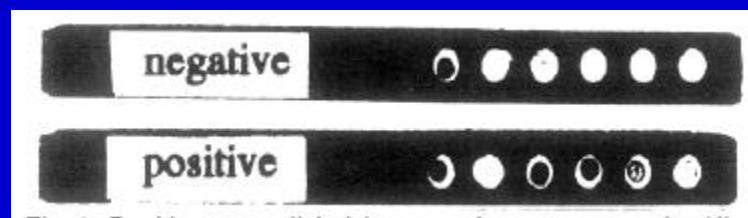
Detection method	No. of positive samples/total no. of samples tested on DAI <sup>a</sup> :																		
	0 <sup>b</sup>	2	4	6	8	10	12	14	16	19	22	25	31	37	44	51	58	64	106
Clinical manifestation <sup>c</sup>				3/3	3/3	3/3	3/3	3/3											
Rickettsial isolation	3/3	2/3	3/3	3/3	3/3	3/3	3/3	3/3	2/3										
PCR amplification (blood) <sup>d</sup>	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	2/3	3/3	2/3	2/3	3/3	



# **Murine Typhus: Laboratory Diagnosis**

## Rapid, simple serodiagnosis of murine typhus

**Khachornsakdi Silpapojakul<sup>1</sup>, Jintana Pradutkanchana<sup>2</sup>, Sukone Pradutkanchana<sup>2</sup> and Daryl J. Kelly<sup>3\*</sup>** *Departments of <sup>1</sup>Medicine and <sup>2</sup>Pathology, Faculty of Medicine, Prince of Songkla University, Songkla, Thailand; <sup>3</sup>Rickettsial and Viral Diseases Program, Naval Medical Research Institute, Bethesda, Maryland, USA*



**Table 3. Sensitivity and specificity of dot-ELISA for the diagnosis of murine typhus**

Cut-off values	Overall sensitivity (%) <sup>a</sup>	Overall specificity (%) <sup>a</sup>	Sensitivity of acute sera (%) <sup>a</sup>
≥4 dots	1.4 (1/74)	100 (47/47)	0.0 (0/27)
≥3 dots	51.4 (38/74)	100 (47/47)	37.0 (10/27)
≥2 dots	89.2 (66/74)	97.9 (46/47)	74.1 (20/27)
≥1 dot	95.6 (71/74)	89.4 (42/47)	88.9 (24/27)

<sup>a</sup>No. of positive sera/no. of sera tested in parentheses.

# MURINE TYPHUS: LATEX AGGLUTINATION TEST

**Table 2. Sensitivity and specificity of the latex agglutination test for the diagnosis of murine typhus**

Cut-off values	Overall sensitivity (%) <sup>a</sup>	Overall specificity (%) <sup>a</sup>	Sensitivity of acute sera (%) <sup>a</sup>
≥ 1:256	85.1 (63/74)	100 (47/47)	66.7 (18/27)
≥ 1:128	86.5 (64/74)	100 (47/47)	70.4 (19/27)
≥ 1:64	87.8 (65/74)	100 (47/47)	74.1 (20/27)
≥ 1:32	93.2 (69/74)	95.7 (45/47)	85.2 (23/27)
≥ 1:16	95.9 (71/74)	95.7 (45/47)	92.6 (25/27)

<sup>a</sup>No. of positive sera/no. of sera tested in parentheses

# Scrub Typhus: Rx

# MICs of Anticlotics Against *O.tsutsugamushi* (Miyamura S et al)

	MICs (range)	Breakpoints Low High	
Tetracycline	0.02 - 0.09	4	16
Doxycycline	0.01 - 0.09	4	16
Minocycline	0.01 - 0.19	4	16
Chloramphenicol	0.19 - 0.39	8	32
Rifampicin	0.005 - 0.09	1	4

# Scrub Typhus: Single Dose Doxycycline Rx

**Patients : 31 Malaysians**

**Fever days before therapy=10.6 days  
(range 4 - 27 d.)**

**Dosage: 200 mg single dose**

**Results: 90 % afebrile within 48 hrs  
100 % afebrile within 96 hrs  
0 % relapse**

*(Ref. : Brown GW et al. Trans R Soc Trop Med Hyg  
1978;72:412-6)*



# TREATMENT OF SCRUB TYPHUS

	3-days Doxycycline	7-days Tetracycline
No.	66	50
Duration of fever		
before treatment	7.7 +/- 4.4 days	7.0 +/- 4.4 days
after treatment	34.0 +/- 26.5 hrs.	37.0 +/- 26.6 hrs .
Relapse	0	0

(Ref : Song JH *et al* : CID 1995 ; 21 : 506 )

## Single dose doxycycline therapy for scrub typhus\*

G. W. BROWN<sup>†</sup>, J. P. SAUNDERS, SADHU SINGH, D. L. HUXSOLL AND A. SHIRAI*United States Army Medical Research Unit, Institute for Medical Research, Kuala Lumpur, Malaysia*‡**Table III—Scrub typhus—comparison of response to treatment**

Treatment group	Afebrile in 48 hr or less	Disappearance of symptoms* means days (range)		
		Headache	Cough	Malaise
<b>Doxycycline</b>	28/31 90%	3·1 (1-6)	3·2 (1-7)	3·8 (1-10)
<b>Tetracycline</b>	19/24 79%	3·2 (1-6)	3·4 (1-10)	3·9 (2-10)

# TREATMENT OF SCRUB TYPHUS

	<b>Chloramphenicol (3 - 6 days)</b>	<b>Tetracycline (3 - 9 days)</b>
<b>No.</b>	<b>30</b>	<b>30</b>
<b>Mean days of illness (before Rx)</b>	<b>4.7</b>	<b>3.9</b>
<b>Afebrile in 24 hrs .</b>	<b>10 (33 %)</b>	<b>23 (77 %)</b>
<b>Afebrile in 48 hrs .</b>	<b>29 (97 %)</b>	<b>29 (97 %)</b>
<b>Relapse</b>	<b>5</b>	<b>2</b>

*(Ref: Sheehy TW et al. Arch Intern Med 1973;132:77 )*

## Scrub typhus infections poorly responsive to antibiotics in northern Thailand

*George Watt, Charoen Chouriyagune, Ronnatrai Ruangweerayud, Pochaman Watcharapichat, Duangporn Phulsuksombati, Krisada Jongsakul, Paktiya Teja-Isavadharm, Dharadhida Bhodhidatta, Kevin D Corcoran, Gregory A Dasch, Daniel Strickman*

Strain of <i>R. tsutsugamushi</i>	Doxycycline		
	0 µg/mL	4 µg/mL	16 µg/mL
<b>Chlangral</b>			
C1	46% (42-49)	3% (2-5)	<1% (0-1)
<b>C3</b>	24% (21-28)	<b>26% (22-29)</b>	5% (3-7)
C27	43% (39-47)	15% (11-18)	1% (0-2)
<b>Karp</b>	39% (36-43)	<b>2% (1-3)</b>	<1% (0-1)

Table 3: Doxycycline susceptibility testing in mouse fibroblast cell culture: mean percentage of L929 cells which contain rickettsia after 30 h (95% CI)

Strain of <i>R tsutsugamushi</i> (1000 MLD <sub>50</sub> )	Antibiotic		
	Chloramphenicol	Doxycycline	None
Chlangral			
C1	7 (47%)*	15 (100%)	0 (0%)
C3	7 (47%)	10 (67%)*	0 (0%)
C27	9 (60%)	10 (67%)*	0 (0%)
Karp	14 (93%)	15 (100%)	1 (7%)

\* Mouse survival significantly lower in Chlangral strain than in Karp ( $p < 0.05$ ; Fisher exact test).

Table 2: Antibiotic susceptibility testing in mice (15 per group). The number (percentage) of mice surviving at day 24 is given for each treatment

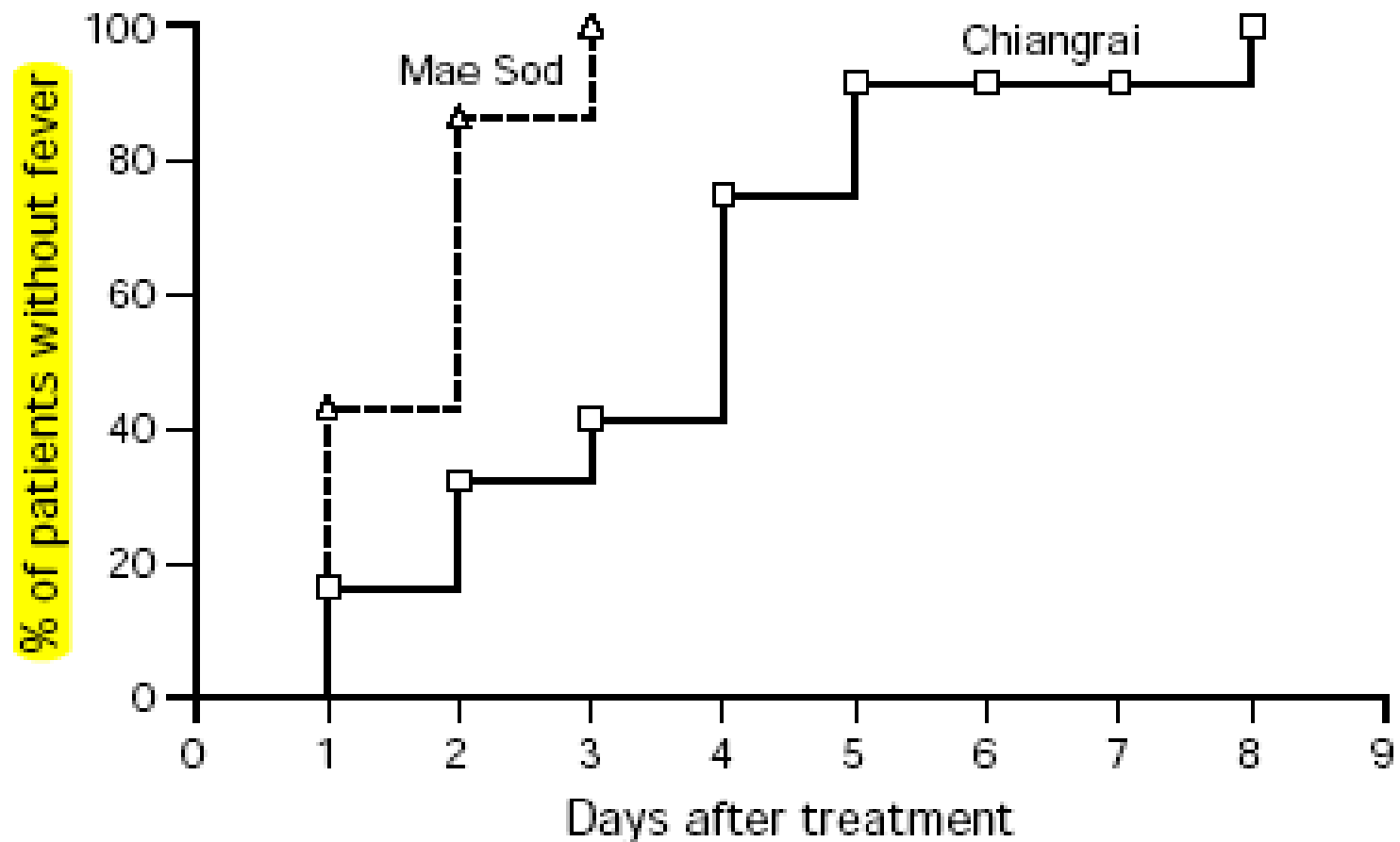


Figure: The percentage of patients in Chiangrai (solid line) and Mae Sod (dotted line) who remain febrile (oral temperature  $>37.2^{\circ}\text{C}$ ) after doxycycline treatment was begun

# Patients & Outcome

**12 from Chiangrai ,7 from Mae Sod**

**Presented during the first week of illness.**

**Mild scrub typhus.**

**Rx with a seven-day course of po.doxycycline**

**All survived and were discharged.**



**Clinical Study of 20 Children with Scrub Typhus at  
Chiang Rai Regional Hospital  
*J Med Assoc Thai 2005;85:1867-72***

Chulapong Chanta MD\*,  
Suwalee Chanta MD\*\*

**20 patients ( 4 with pneumonitis, 2 with pneumonitis plus pulmonary edema and 1 with pneumonitis plus shock, 1 with encephalitis).**

**Those who were Rx with chloramphenicol (14 patients) or doxycycline(2 patients) were afebrile within 72 hrs. and recovered well.**

# Doxycycline and rifampicin for mild scrub-typhus infections in northern Thailand: a randomised trial

***Lancet;2000;356:1057-61***

George Watt, Pacharee Kantipong, Krisada Jongsakul, Pochaman Watcharapichat, Duangporn Phulsuksombati, Daniel Strickman

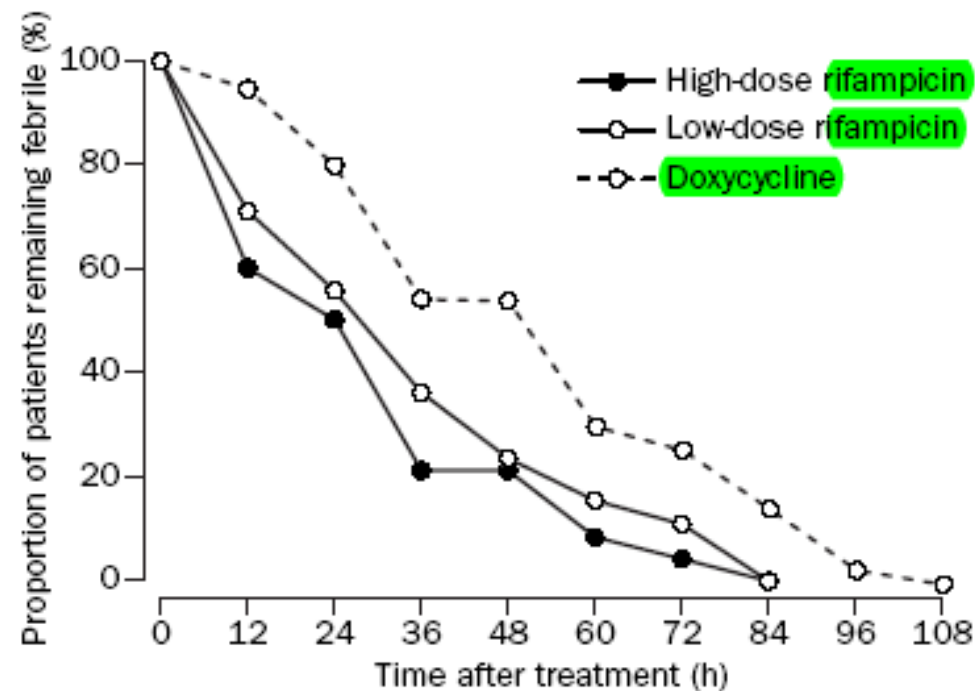


Figure 3: Proportions of patients remaining febrile after treatment

# SCRUB TYPHUS - AZITHROMYCIN

In - vitro study showed that azithromycin was more effective than doxycycline against both the Karp strain and a doxycycline - resistant Thai (AFSC - 4) strain .

(Ref.: Strickman D *et al.* AAC 1995,39: 2406)

# A Comparative Trial of a Single Dose of Azithromycin versus Doxycycline for the Treatment of Mild Scrub Typhus

Yeon-Sook Kim,<sup>1</sup> Hwan-Jung Yun,<sup>2</sup> Soo Kyoung Shim,<sup>5</sup> Sun Hoe Koo,<sup>4</sup> Sun Young Kim,<sup>3</sup> and Samyong Kim<sup>2</sup>

***CID 2004;39:1329-35***

**Table 2. Outcomes of patients who received azithromycin or doxycycline for the treatment of scrub typhus.**

Outcome	Treatment group	
	Azithromycin (n = 47)	Doxycycline (n = 46)
Cure	47 (100)	43 (93.5)
Failure	0	3 (6.5)
Relapse	0	0
Time to defervescence, median h (range)	21 (1–120)	29 (4–176)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Comparison of the 2 groups with respect to each outcome revealed **no significant differences** ( $P > .05$ ).

# Scrub Typhus & New Macrolides

**: Three cases of scrub typhus were successfully treated with clarithromycin, all became afebrile within 2 - 3 d.**

**: Dosage used = 400 mg/day for 12 - 20 d .**

**(Miura N et al: Acta Med Nagasaki 1996 ; 40 : 44)**

# MICs of Quinolones against *O. tsutsugamushi* (Miyamura et al)

	MICs (range)	Breakpoints Low High	
Norfloxacin	50 - 100	4	16
Ciprofloxacin	6.25 - 25	1	4
Ofloxacin	3.12 - 25	2	8

COMPARISON OF THE EFFECTIVENESS OF FIVE DIFFERENT ANTIBIOTIC  
REGIMENS ON INFECTION WITH *RICKETTSIA TYPHI*: THERAPEUTIC DATA  
FROM 87 CASES

ACHILLEAS GIKAS, STEPHANOS DOUKAKIS, JOHN PEDIADITIS, SERAFIM KASTANAKIS, ANDREAS MANIOS, AND  
YIANNIS TSELENTIS

TABLE 2

Antibiotics used in 87 patients with *Rickettsia typhi* infection

Treatment	No. of patients (%)	Days of fever (mean)	SD
Doxycycline *	29 (33.3)	2.89 *	1.23
Ciprofloxacin	14 (16.0)	4.23	2.07
Chloramphenicol	12 (13.7)	4.00	1.07

\*  $P < 0.05$



# Rickettsioses & Complications

## **Case 18 (Nom, 149108)**

**F 49 yrs, farmer from Rat-ta-pum**

**CC : Had fever for 10 days**

**Hx : Fever with myalgia and chest pain for 10 days  
developed dyspnea 2 days P.T.A.**

**PE : T 38 °C tachypnic 30 /min. HR120 BP 80/50**

**Neck veins not engorged.**

**Lungs : crepitation both lower lung fields**

**Liver 4 cm. Below RCM.**

**Skin : Rt. Groin**



**Lab : Hct 29%, WBC 12,450, P 85%, L 15%**

**Malaria = negative UA = WNL**

**Serum creatinine 3.3 mg%, BUN 75 mg%**

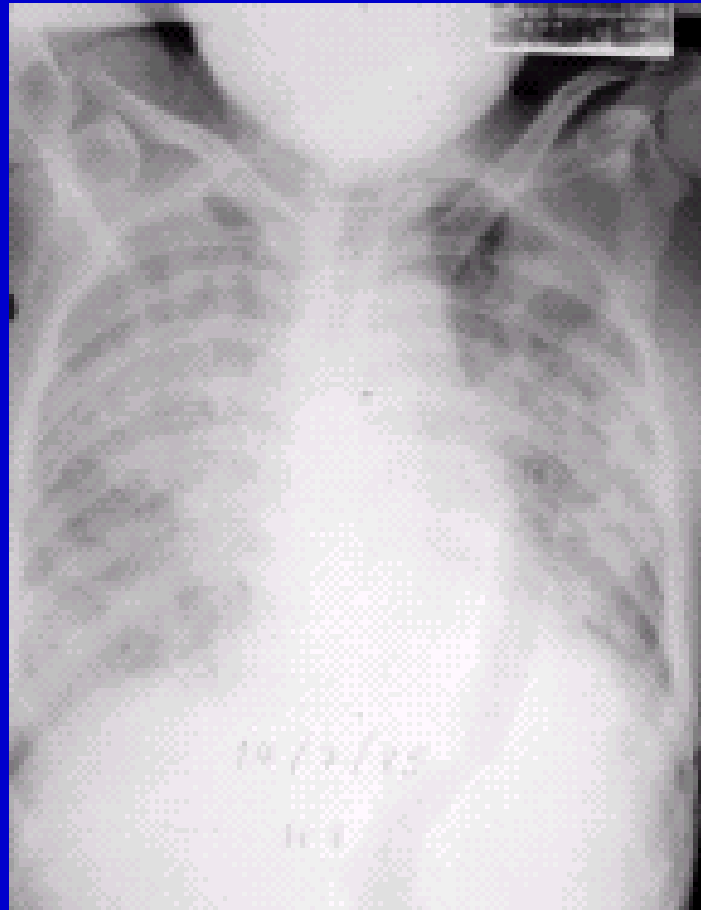
**Bilirubin = 2.1 mg% total**

**SGOT 98 IU. SGPT 53 IU.**

**Alk. Phos. 160 IU.**

**EKG = WNL**

**CXR**



**Nom 14/7/85**

**Lab :CSF = WBC = 9 (all = mono) glucose = 70  
Prot = 140**

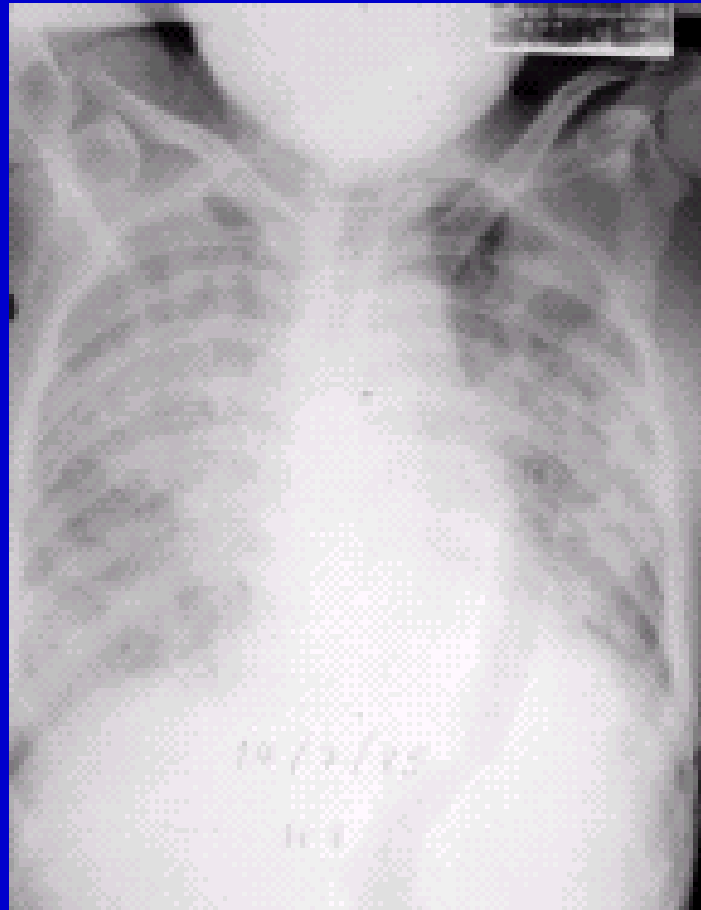
**Blood & urine culture = negative**

## Serology :

	15/7/85	normal
OXK	1:1,280	< 1:160
OX-2	1:40	< 1:40
OX-19	1:80	< 1:80

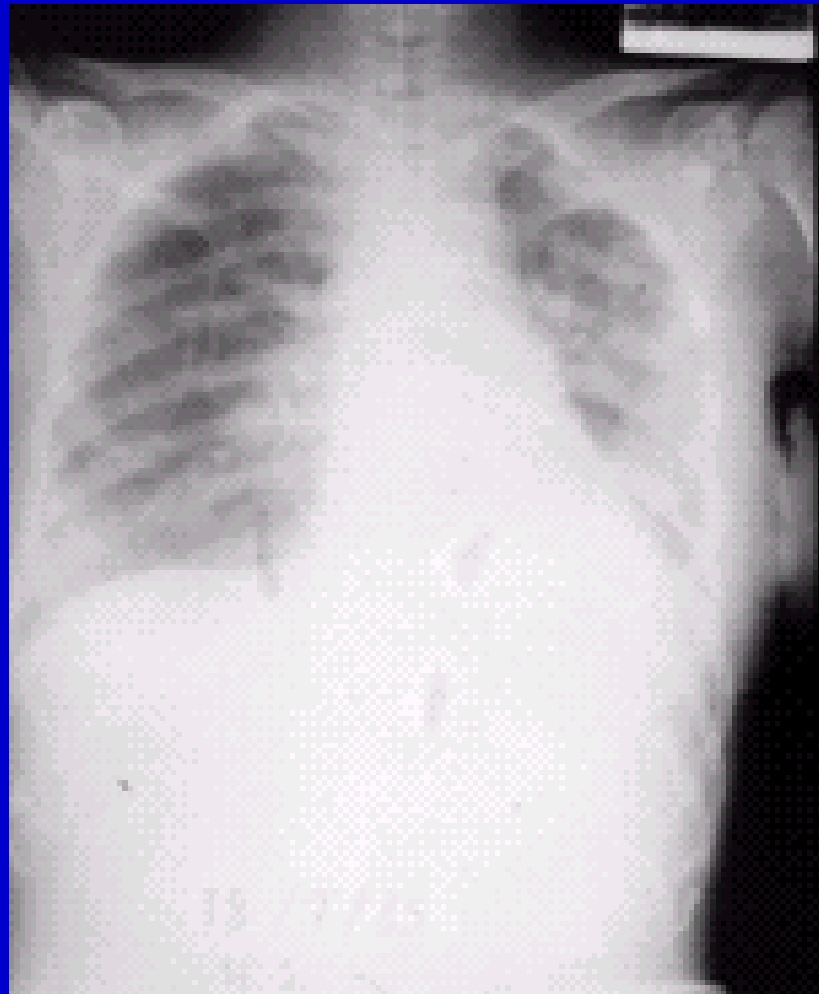
IFA (*R. tsutsugaamushi*) = > 1:2,560  
(cut point = < 1:400)

Leptospira titer = negative

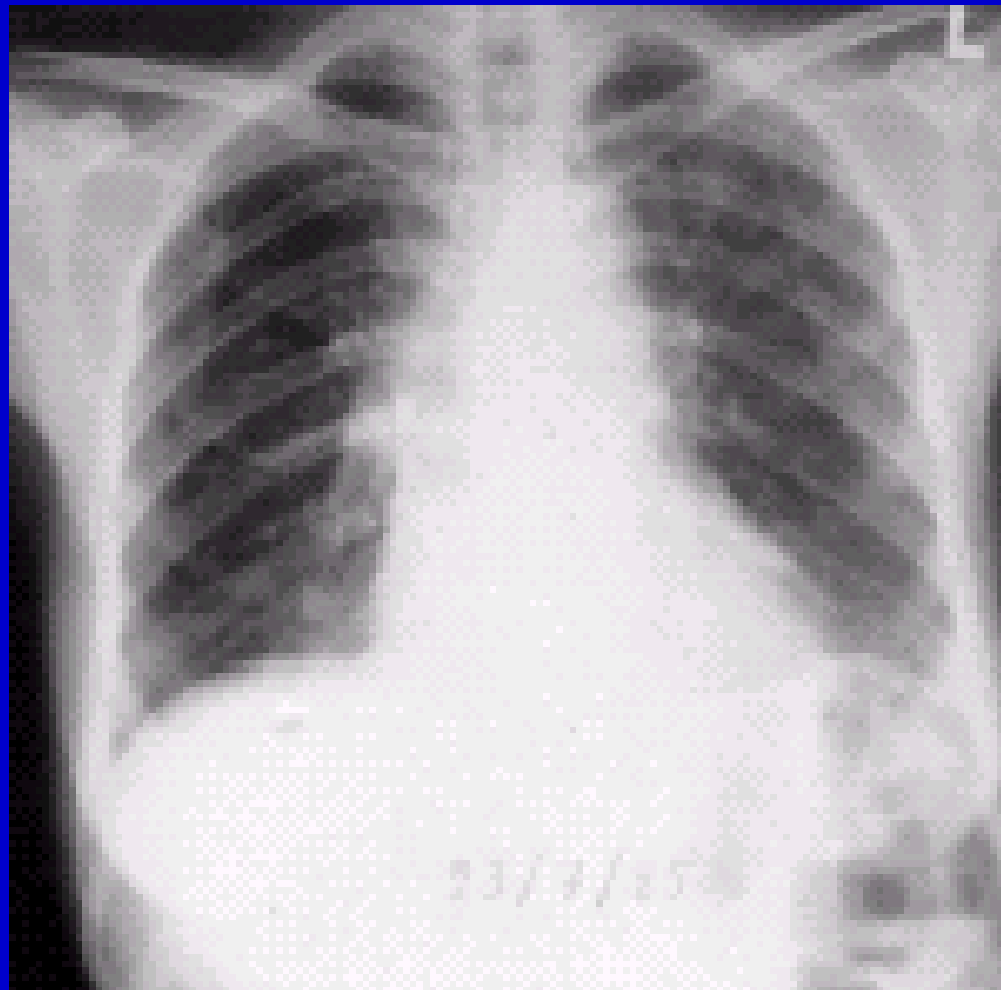


**Nom 14/7/85**





**Nom 18/7/85**



**Nom 23/7/85**

# Serious complications in scrub typhus.

Tsay RW,Chang FY.J Microbiol Immunol Infect.1998;31:240-4.

<b>No. of cases</b>	<b>33 (100%)</b>
<b>Pneumonitis</b>	<b>12 (33%)</b>
<b>ARDS</b>	<b>5 (15%)</b>
<b>Acute renal failure</b>	<b>3 ( 9%)</b>
<b>Myocarditis</b>	<b>1 ( 3%)</b>
<b>Septic shock</b>	<b>1 (3%)</b>

# Complications in scrub typhus.

Song SW et al. J Korean Med Sci. 2004;19(5):668-73.

No. of cases	101 (100%)
<b>Hypoxia</b>	<b>24 (23.8%)</b>
Hypotension	17 (16.8%)
Acute renal failure	15 (14.9%)
Septic shock	2 (1.9%)
Death	4 (3.9%)

# SEPTIC SHOCK SECONDARY TO SCRUB TYPHUS: CHARACTERISTICS AND COMPLICATIONS

Lon Chan Thap<sup>1</sup>, Wichai Supanaranond<sup>2</sup>, Sombat Treeprasertsuk<sup>2</sup>, Sirima Kitvatanachai<sup>3</sup>,  
Soontorn Chinprasatsak<sup>4</sup> and Benjaluck Phonrat<sup>2</sup>

Southeast Asian J Trop Med Publ Health 2002;33:780-6

**7 weeks study at Korat Hospital**

**110 patients had sepsis**

**51/110 patients had septic shock**

**18 (35.3%) had serologic evidence of scrub typhus**

**11/18 had eschar**



**Table 1**  
**Percentage of septic shock: scrub typhus**  
**and other causes.**

<b>Disease</b>	<b>No. of cases (n = 51)</b>	<b>%</b>
<b>Scrub typhus</b>	<b>18<sup>a</sup></b>	<b>35.3</b>
<b>Other causes</b>	<b>33</b>	<b>64.7</b>
<b>Leptospirosis</b>	<b>8</b>	<b>15.7</b>
<b>Typhoid or paratyphoid fever</b>	<b>2</b>	<b>3.9</b>
<b>Melioidosis + leptospirosis</b>	<b>1</b>	<b>2.0</b>
<b>Septic shock with Gram-ve bacteria</b>	<b>8</b>	<b>15.7</b>
<b>Septic shock with Gram+ve bacteria</b>	<b>7</b>	<b>13.7</b>
<b>Liver abscess</b>	<b>1</b>	<b>2.0</b>
<b>Unknown</b>	<b>6</b>	<b>11.8</b>
<b>Total</b>	<b>51</b>	<b>100.0</b>

# Scrub typhus with septic shock

**18 patients**

**14/18 (78%) had abnormal CXRs**

**3 died, all from respiratory failure**

**3 transferred and outcome not mentioned**

**Lon Chan Thap et al. Septic shock secondary to scrub typhus.  
Southeast Asian J Trop Med Publ Health 2002;33:780-6**

## Clinical Role of Interstitial Pneumonia in Patients with Scrub Typhus: A Possible Marker of Disease Severity

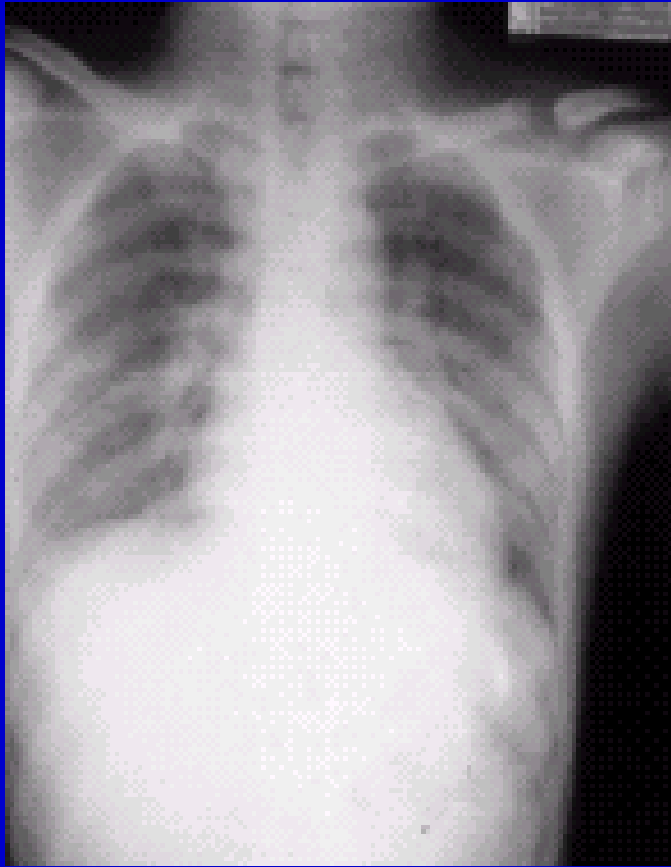
Interstitial pneumonia (IP) frequently occurs in patients with scrub typhus, but its

Sun Wha Song, Ki Tae Kim,

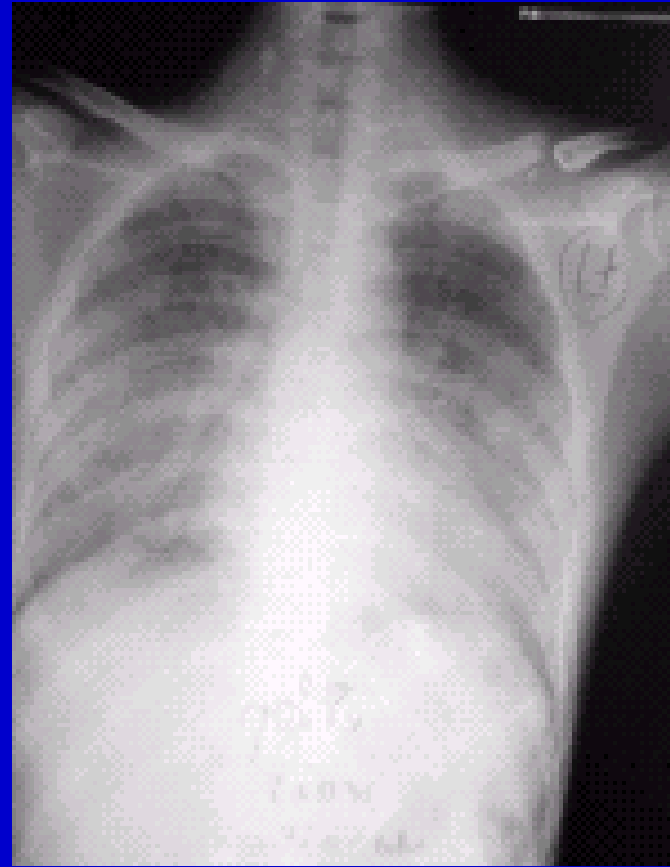
**Abnormal CXRs = 60/101 (59.4%)**

**52/60 (87%) = interstitial infiltration**

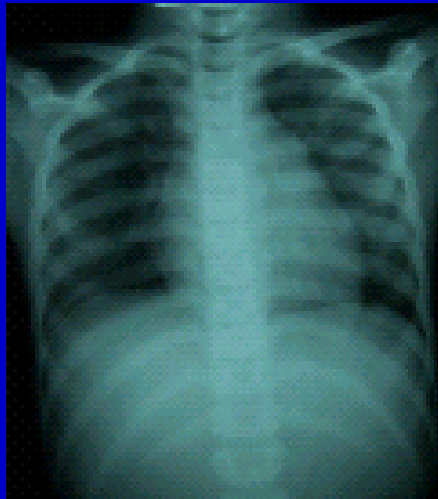




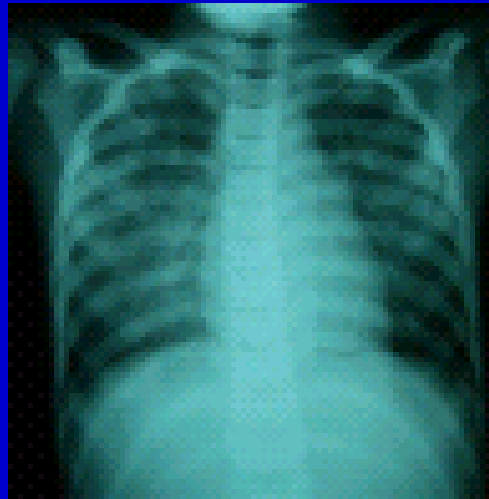
**WJ. 7/8/1992**



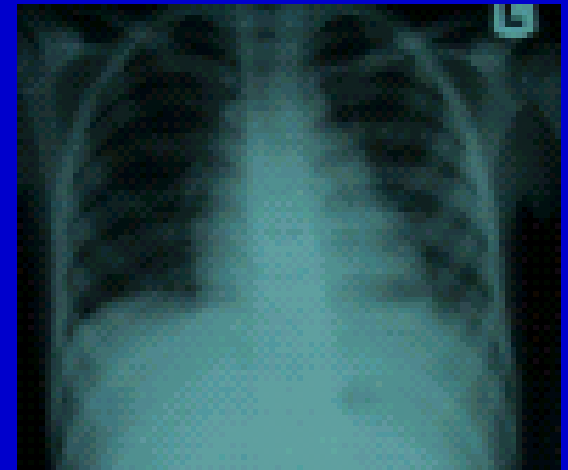
**WJ. 8/8/1992**



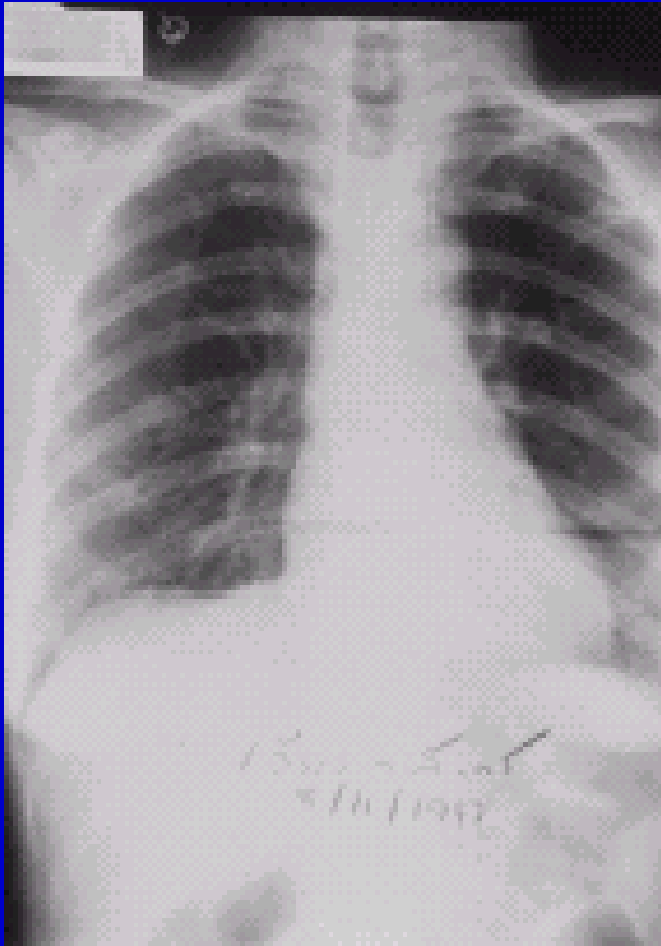
**31 Jul 2000**



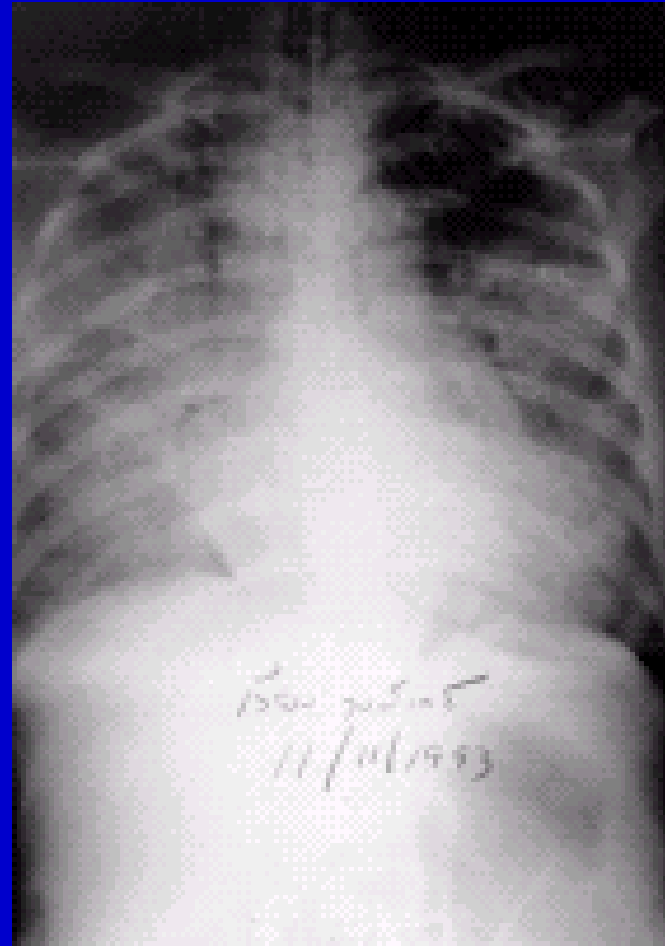
**1 Aug 2000**



**5 Aug 2000**



**8 Nov 1993**



**11 Nov 1993**

# ARDS in scrub typhus

**36% (12/33) had pneumonitis.**

**42% (5/12) progressed to ARDS.**

**Median duration of symptoms=9 d.**

**(only one < 7 d.).**

**eschar=4/9**

**skin rash=3/9**

**Hepatosplenomegaly=5/9.**

**Normal WBC count=7/9**

**Thrombocytopenia=8/8**

# Rickettsial Pneumonitis : Summary

**1. Severe form usually developed in the elderly, after the first week and commonly accompanied by either jaundice, renal failure or meningitis**

**2. Less severe form commonly misdiagnosed as mycoplasma pneumonia (D/Dx clues : age, eschar, effusion)**

**3**

**. 3.Children and pregnant patients commonly were tachypnic.**

**4.Another clue: tachypnea or oxygen desaturation in the pressence of minimal interstitial infiltration.**

**5. Rapid change of pulmonary infiltrate.**

# ARDS in Scrub Typhus: Other organs involvement

**Table 1** Clinical characteristics of patients with acute respiratory distress syndrome complicating scrub typhus

Patient	Reference	Age/sex	Skin rash/eschar	Associated complications	Days of symptoms before antibiotic	Outcome
1	PR	61/F	-/+	Multi-organ failure	9	Died
2	PR	21/M	+/-	Myocarditis with AV dissociation, DIC	7	Survived
3	PR	25/M	+/-	No	7	Survived
4	PR	23/M	-/-	No	10	Survived
5	PR	65/F	-/+	No	7	Survived
6	4	61/F	-/+	Multi-organ failure	4	Died
7	4	62/F	-/+	No	11	Survived
8	3	21/M	+/-	Meningoencephalitis, septic shock	11	Survived
9	5	48/M	-/-	Tubulointerstitial nephritis with acute renal failure, UGI bleeding, DIC	19	Survived

Tsay RW, Chang FY. QJM 2002;95:126

**“Despite the occurrence of serious complications, good response to antibiotic therapy was obtained and the average duration of defervescence was 2 days. Mortality was 22% (2/9) in this review. The major cause of mortality was delay in diagnosis.”**