African tick typhus

David Mabey

25 year old English man
Holiday in Zimbabwe for 3 months
Became unwell on plane home

- Fever
- Rash
- Generalised lymphadenopathy

This photo was taken 2 days after onset of symptoms

Travel History is important

Where exactly has the patient been?

- **Which countries?**
- **Rural or urban?**
- **Dates of travel, when did symptoms begin?**

What exactly has the patient been doing?

- **New sexual partner(s)?**
- **Fresh water contact?**
- **Exposure to sick people?**

Immunisations before travel?

Malaria prophylaxis?

Any other medication or past medical history?

25 year old English man

Fever and rash 4 days

Holiday for 2 weeks in South Africa

Returned 2 days ago

Visited Kruger game park

Travelled with his wife

Physical Exam is important

Eschar in African tick typhus

African tick typhus

- Caused by *Rickettsia africae*
- Transmitted by ticks (*Amblyomma* sp.)
- Found throughout sub-Saharan Africa
- Common in Southern Africa
- Often seen in tourists who have visited game parks in Southern Africa
- Also endemic in West Indies

Clinical features

- Fever
- Rash in about 50% of cases
  - Usually maculopapular
  - May be vesicular
- Eschar in > 50% of cases
  - May be multiple
  - Often with regional lymphadenopathy

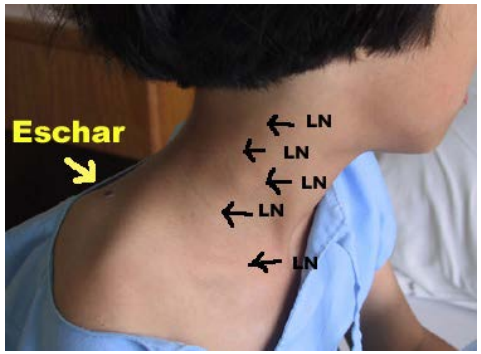
Investigations

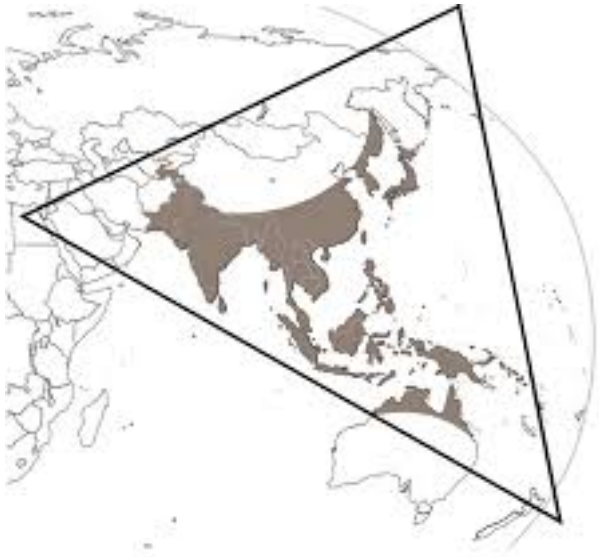
- May be low platelets, raised liver enzymes
- Serology (immunofluorescence) (not highly specific)
- PCR

Treatment

- Doxycycline 200mg daily for 1-7 days
- Azithromycin 20mg/kg single dose for children and pregnant women
- Rapid response to treatment

Scrub typhus





A 60 year old farmer presents to your hospital

- 60 year old farmer
- Presents with 7 days of fever and 2 days of dry cough
- On examination: temperature 39^{o}C, icterus, hypotensive (BP: 90/55) course crackles in right lower zone, confused
- Blood tests: neutropenia, thrombocytopenia, ALT 300 IU/ml and acute kidney injury
- Negative tests for malaria + dengue
- What else do you want to know?
- What would you do?

Scrub Typhus

- *Orientia tsutsugamushi*
- *Leprotrombidium* mites
  - Larvae infect
  - Adults maintain infection
    - Transovarial spread
- Disease similar to louse-borne typhus (lower mortality rate)
- ~1 million cases/year (massively underdiagnosed)
- Maintained in a rodent-mite life-cycle
- ‘Mite islands’ (areas of focal and intense transmission)
- Occasionally bite larger mammals such as humans

Causes of non-malarial fever in Laos: a prospective study

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Summary

Background Because of reductions in the incidence of *Plasmodium falciparum* malaria in Laos, identification of the causes of fever in people without malaria, and discussion of the best empirical treatment options, are urgently needed. We aimed to identify the causes of non-malarial acute fever in patients in rural Laos.

Methods For this prospective study, we recruited 1938 febrile patients, between May, 2008, and December, 2010, at Luang Namtha provincial hospital in northwest Laos (n=1390), and between September, 2008, and December, 2010, at Salavan provincial hospital in southern Laos (n=548). Eligible participants were aged 5–49 years with fever (≥38°C) lasting 8 days or less and were eligible for malaria testing by national guidelines.

Findings With conservative definitions of cause, we assigned 799 (41%) patients a diagnosis. With exclusion of influenza, the top five diagnoses when only one aetiological agent per patient was identified were dengue (156 [8%] of 1927 patients), scrub typhus (122 [7%] of 1871), Japanese encephalitis virus (112 [6%] of 1924), leptospirosis (109 [6%] of 1934), and bacteraemia (43 [2%] of 1938). 115 (32%) of 358 patients at Luang Namtha hospital tested influenza PCR-positive between June and December, 2010, of which influenza B was the most frequently detected strain (n=121 [87%]). Disease frequency differed significantly between the two sites: Japanese encephalitis virus infection (p=0·04), typhoid (p=0·006), and leptospirosis (p=0·001) were more common at Luang Namtha, whereas dengue and malaria were more common at Salavan (all p<0·0001). With use of evidence from southeast Asia when possible, we estimated that azithromycin, doxycycline, ceftriaxone, and ofloxacin would have had significant efficacy for 258 (13%), 240 (12%), 154 (8%), and 41 (2%) of patients, respectively.

Interpretation Our findings suggest that a wide range of treatable or preventable pathogens are implicated in non-malarial febrile illness in Laos. Empirical treatment with doxycycline for patients with undifferentiated fever and negative rapid diagnostic tests for malaria and dengue could be an appropriate strategy for rural health workers in Laos.

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See Comment page e11

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Introduction

Increased use of rapid diagnostic tests for malaria in Laos has shown that many individuals with suspected malaria are not infected with *Plasmodium falciparum* or *Plasmodium vivax*. Although the incidence of falciparum malaria is falling, transmission is heterogeneous between regions, with higher incidence in the south than in the north.[1] Therefore, a major clinical question paradoxically arises as malaria diagnosis improves: what are the main diagnoses among febrile patients without malaria and how should these individuals be treated?

What treatment patients without malaria receive at all levels of health care in rural Laos is left to health workers to decide. However, few diagnostic facilities or data are available to identify the pathogens responsible, or their antimicrobial susceptibility patterns, to guide these decisions. A wide range of infectious diseases have been described from Laos, including typhoid, scrub typhus (*Orientia tsutsugamushi*), murine typhus (*Rickettsia typhi*), *Neorickettsia sennetsu*, dengue, leptospirosis, Japanese encephalitis virus, and influenza.[2–11] However, most of these data are from Vientiane where no malaria transmission takes place.[1] In malaria-endemic regions of Laos, village health volunteers are trained to undertake rapid diagnostic tests for malaria and to give antimalarial drugs to patients who test positive. Most results are negative, thus information is needed to develop algorithms to manage febrile patients with no malaria. To be effective, such algorithms should take into account heterogeneity in incidence and epidemiology of infectious disease across a country, because to base empirical treatment on a country-wide protocol could reduce effectiveness.[12] We therefore did a prospective investigation of the causes of acute fever in patients tested for malaria in northern and southern Laos.

Methods

Study design and participants

We did this prospective study at Luang Namtha provincial hospital in northwest Laos between May 2,

Scrub Typhus Distribution

Scrub typhus – clinical features

- Incubation – 12 days (6-12)
- Eschar at bite site
- Fever, headache, retrobulbar pain
- Myalgia
- Maculopapular rash
- Severe complications: hepatic failure, renal failure, meningoencephalitis, pneumonitis, pulmonary oedema
- Severe features more common in older patients
- Leukopenia/leukocytosis/NAD
- Mortality – ~6%
- Disease duration ~ 14-21 days

FIGURE 43.—Typical eschar seen in scrub typhus indicates site of infection by the trombi-culid mite. The lesion, generally up to 1 cm in diameter, consists of a central tough black scab surrounded by a slightly elevated, dull red areola; it is neither painful nor pruritic. (Courtesy, Carlton Reiley, M.D.)

Scrub Typhus – differential diagnosis

- Other rickettsial diseases
  - Louse-borne typhus
  - Murine typhus
- Dengue, chikungunya
- Leptospirosis
- Diagnosis –
  - Clinical “doxycycline-responsive fever”
  - Immunofluorescence – poorly available (results affected by background immunity)
  - Rapid tests: dot blot immunoassay dipstick is being evaluated
  - Culture…~4 weeks, class 3
  - PCR (often not available where it is needed)

FIGURE 44.—Maculopapular rash showing dull red, discrete macular eruptions appearing first on the trunk and spreading to arms, legs, and face. (Courtesy, Carlton Reiley, M.D.)

Scrub Typhus - Treatment

- Relatively under researched
- Doxycycline 200mg/day 5-7 days
- Azithromycin 500mg – 1g/day for 1-3 days (use in pregnancy)
- Rifampicin 300mg bd 7 days
- Chloramphenicol 3g/day for 3 days
- Concerns that shorter courses are associated with relapse
- Questions: ?combination therapy, ?chemoprophylaxis

Murine typhus
Rickettsia typhi

AKA

Endemic typhus

Fleaborne typhus

R typhi

Small, Gram negative obligate intracellular bacteria

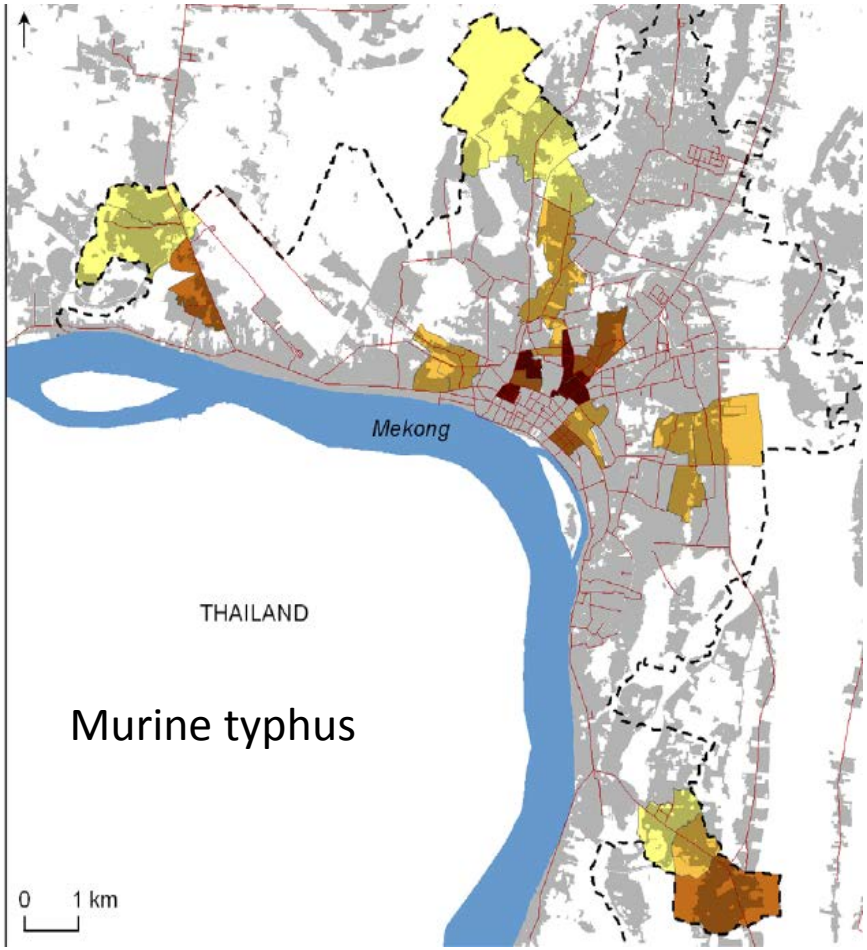
Transmitted by rat fleas *(Xenopsylla cheopis)* & cat fleas *(Ctenocephalides felis)*

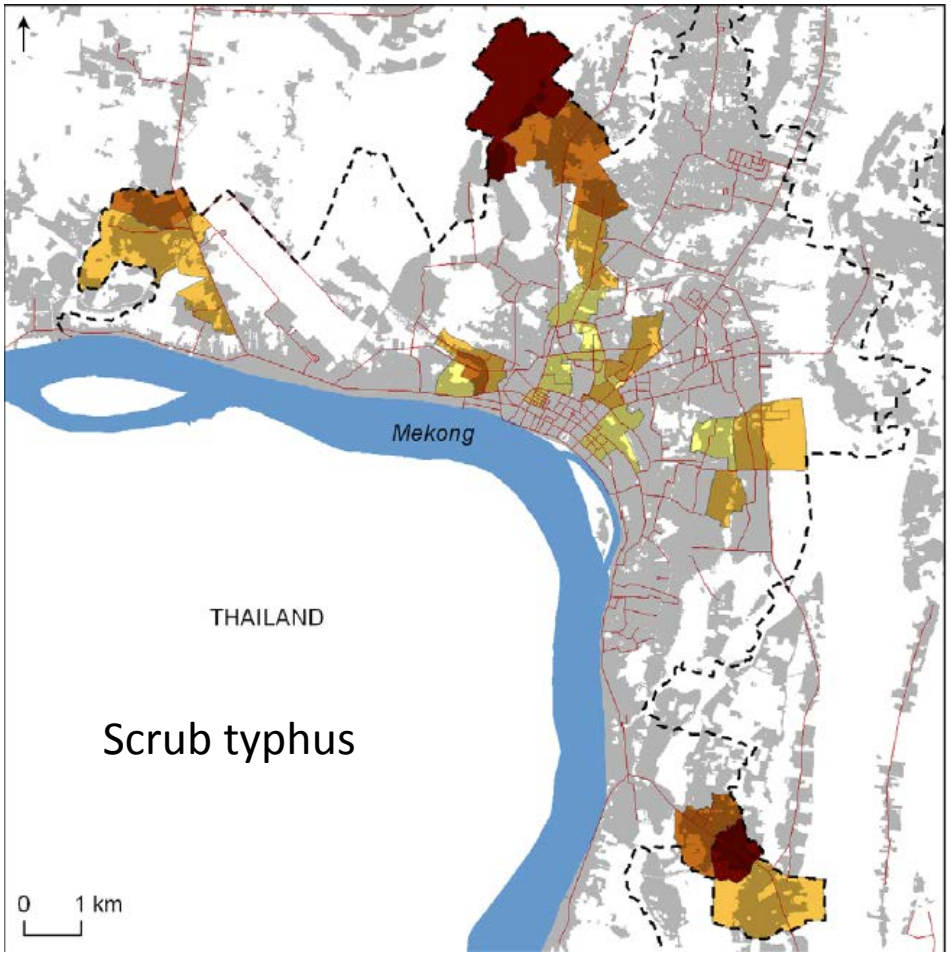
Epidemiology

Globally disseminated disease

Urban & suburban distribution (*cf* scrub)

Prevalence of IgG in Adults: Vientiane, Lao PDR





Vallee et al PloS NTD 2010; 4(12)

Epidemiology

Globally disseminated disease

Urban & suburban distribution (*cf* scrub)

Common cause of undifferentiated fever in urban centres in SEA (Hamaguchi *et al* AJTMH 2015)

Good data rare due to clinical picture

Clinical Characteristics

Fever (98 – 100%)

Headache (40 – 90%)

Rash (20 – 80%; often after 7d fever)

Arthralgia (40-77%)

Confusion (2- 13%)

Usually no eschar

Civen & Ngo, CID 2008; 46

Lab findings

Anaemia (18-75%)

Raised or reduced WCC

Low platelets (19-48%)

Raised liver enzymes (40-90%)

Civen & Ngo, CID 2008; 46

Diagnosis & Treatment

Diagnosis
Usually clinical
Serial IFA (perhaps ELISA)
PCR (buffy coat)
Culture in specialist centers

Treatment
Doxycycline
Chloramphenicol
?Azithromycin

Summary

Disease	Tick	Flea	Louse	Mite
Scrub Typhus				*O tsutsugamushi*
Typhus		*R typhi*	*R prowazekii*	
Spotted Fever	*R rickettsii*	*R felis*		*R akari*
	R conorii			
	R japonica			
	R australis			
	R honei			
	Etc.			

Conclusions

Rickettsial infection remains a challenging diagnosis

Very few data on returning travellers

Clinical suspicion and trial of treatment

Few clinical studies on appropriate management