Typhus case discussions

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Imported Fever Service (PHE/LSTM/LSHTM)

Conflict of interest statement

- No conflicts to declare. All opinions are my own and not necessarily those of the NIHR, PHE etc

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- Prof Ranjan Premaratna, University of Kelaniya, Colombo, Sri Lanka
- Dr Gerry Davies, University of Liverpool
- Drs Laura Nabarro & Kate Woods IFS
- Dr Sarah Meisner, Bath
- Dr Madur Sudhanva, Kings London

Scope of talk

- Introduction
- Cases
- Summary of points
- Sources

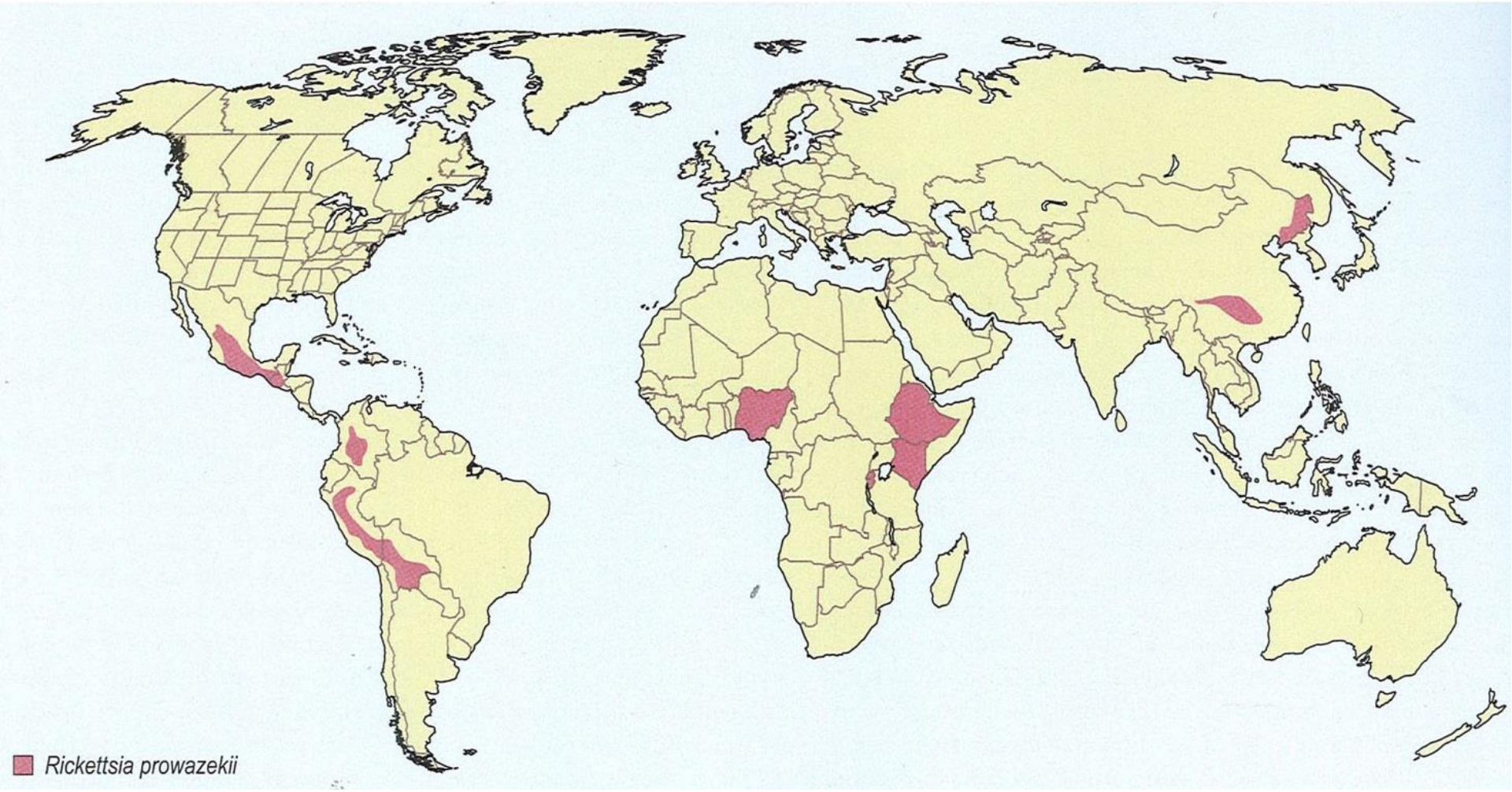
Rickettsial diseases

- Epidemic louse-borne fever
- Brill-Zinsser disease
- Endemic murine typhus

} "Typhus" group proper

- Spotted Fevers (Tick typhus)
- Scrub typhus (Orientia)
- Rickettsial pox
- Q fever (Coxiella Burnetii)
- Bartonellosis

Louse borne typhus

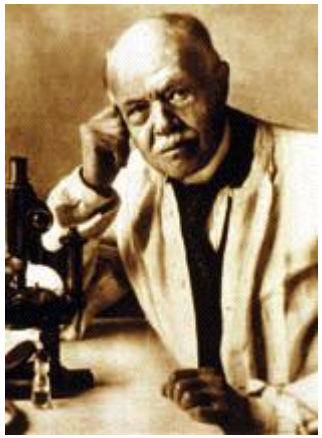


Walker DH, Raoult D. Ch50 in Guerrant RL *et al* *Tropical Infectious Diseases* 3rd ed. Elsevier 2011

Louse borne typhus *R prowazekii*

Pediculus humanus var. *corporis*

Vector of *R. prowazekii*



Charles Nicolle

Hans Zinsser

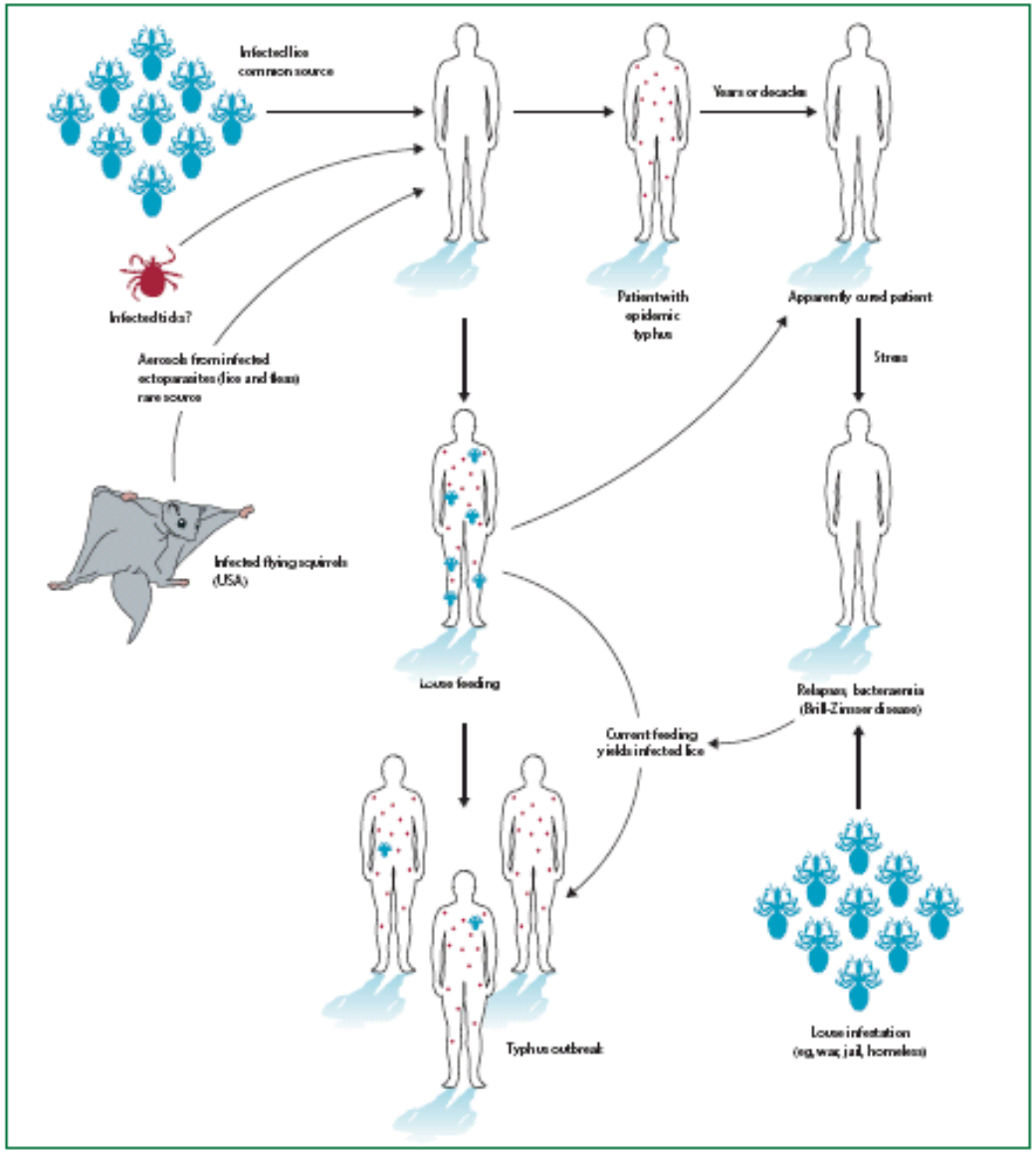


Figure 3: Life cycle of *R prowazekii*

Clinical features : epidemic louse borne typhus

Incubation period 5-23 days

(average 12)

Abrupt onset

High sustained fever resolved by crisis

after 7-14 days

Lethargy and stupor

Truncal macular/petechial rash

Small and large vessel infarction

Headache, meningoencephalitis

Myocarditis

Mortality approx 20%

Case 1

Male age 45

Returned from two weeks in South India

Urban living – Chennai

3 days

Headache

Fever

Malaise

1 day

Rash

Traveller returning from urban India

Traveller returning from urban India

Tests

Hb 125

WCC 4.2

Lymph 0.8

Platelets 127

ALT 56

Diagnosis?

HIV

Murine typhus

Scrub typhus

Syphilis

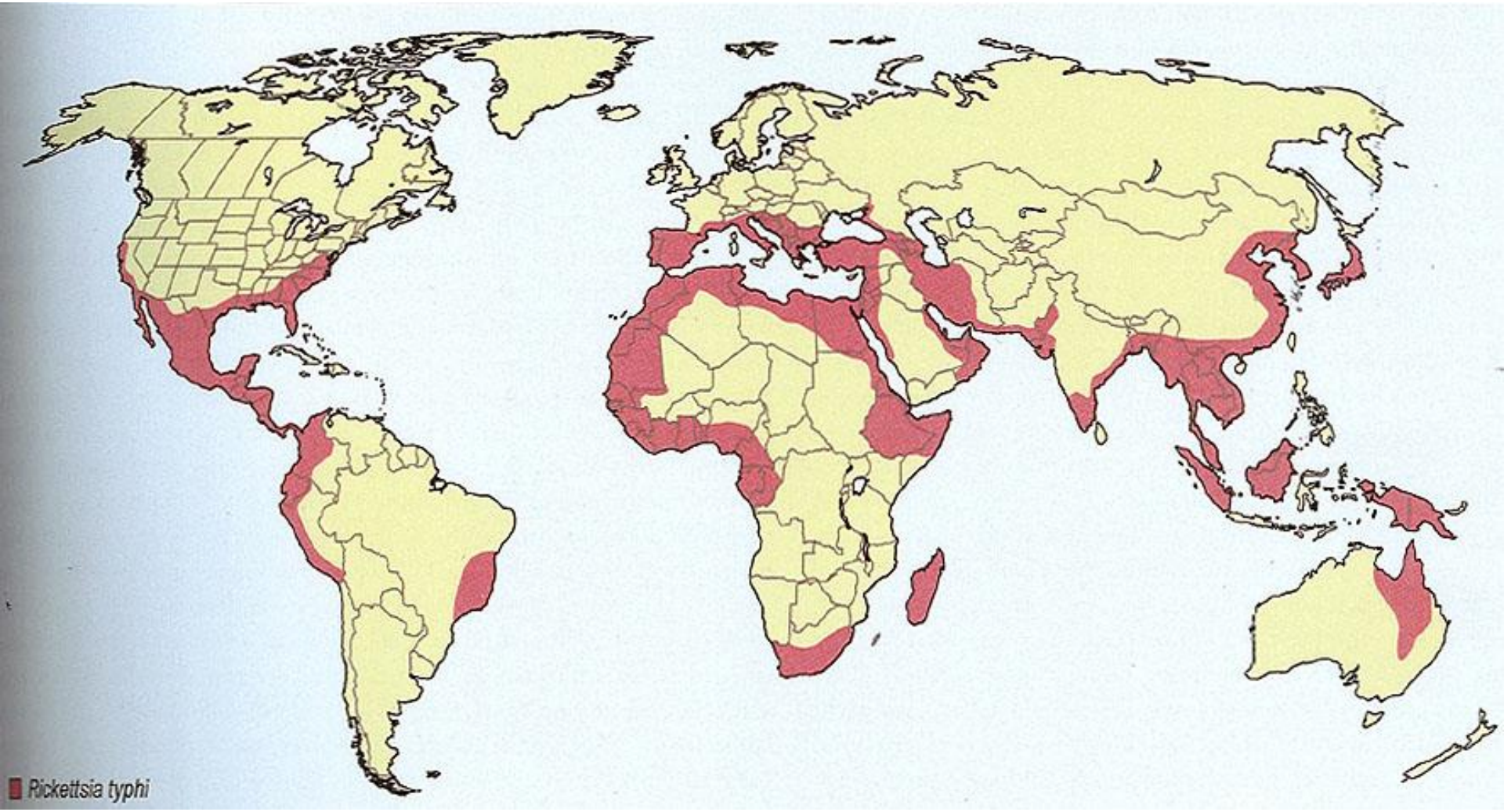
Tick typhus

Other

Diagnosis

Serology suggestive murine typhus (*R typhi*)

Murine typhus

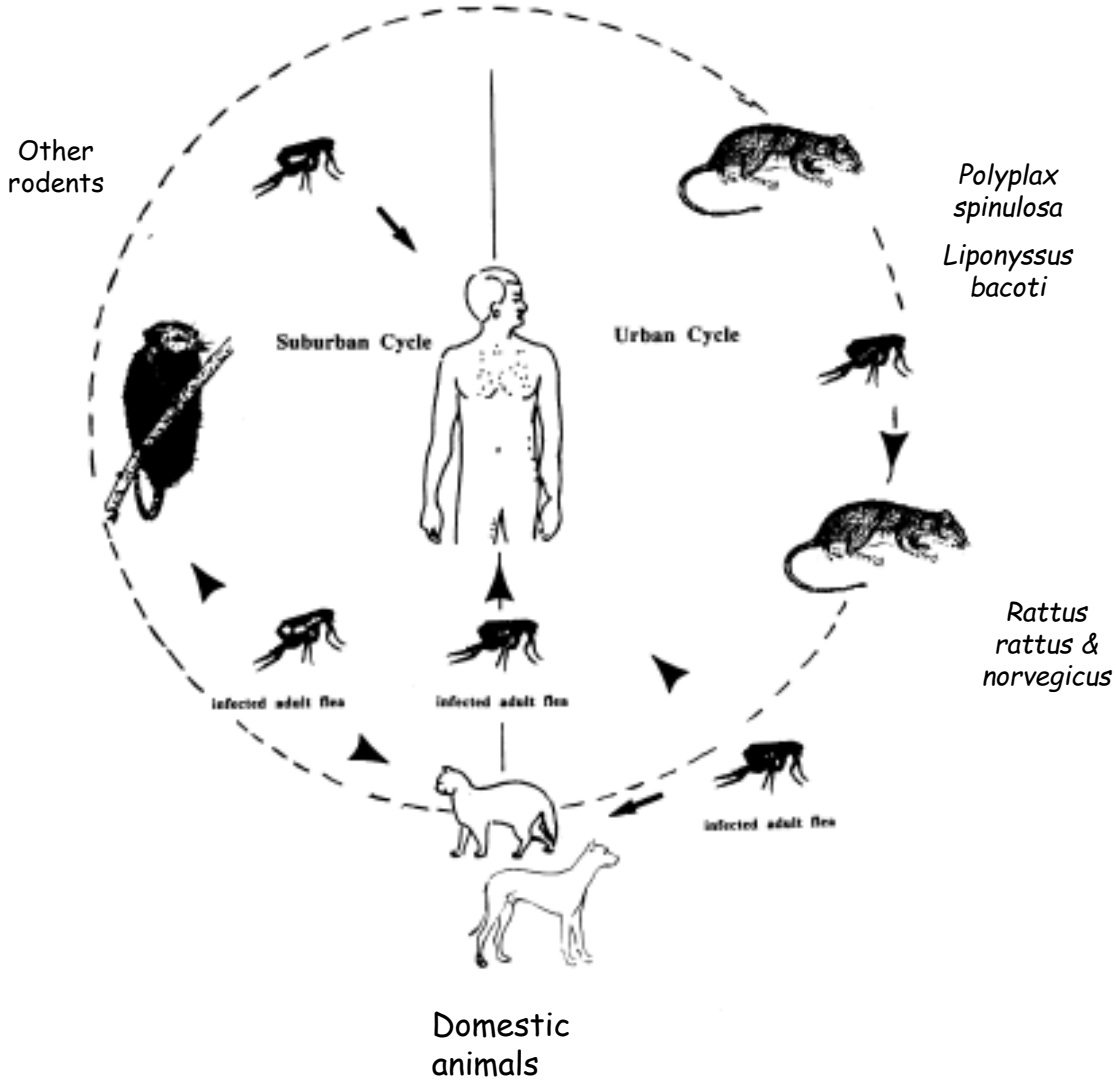


Walker DH, Raoult D. Ch50 in Guerrant RL *et al* *Tropical Infectious Diseases* 3rd ed. Elsevier 2011

Murine typhus *R. typhi*

***Xenopsylla cheopis* (rats)**

Vector of *R. typhi*



Civen R *CID* 2008

INVITED ARTICLE CLINICAL PRACTICE

Ellie J. C. Goldstein, Section Editor

Murine Typhus: An Unrecognized Suburban Vectorborne Disease

Rachel Civen and Van Ngo

Acute Communicable Disease Control Program, Los Angeles County Public Health Department, Los Angeles, California

Murine typhus, an acute febrile illness caused by *Rickettsia typhi*, is distributed worldwide. Mainly transmitted by the fleas of rodents, it is associated with cities and ports where urban rats (*Rattus rattus* and *Rattus norvegicus*) are abundant. In the United States, cases are concentrated in suburban areas of Texas and California. Contrary to the classic rat-flea-rat cycle, the most important reservoirs of infection in these areas are opossums and cats. The cat flea, *Ctenocephalides felis*, has been identified as the principal vector. In Texas, murine typhus cases occur in spring and summer, whereas, in California, cases have been documented in summer and fall. Most patients present with fever, and many have rash and headache. Serologic testing with the indirect immunofluorescence assay is the preferred diagnostic method. Doxycycline is the antibiotic of choice and has been shown to shorten the course of illness.

Table 1. Studies reporting clinical findings associated with murine typhus.

Civen R *CID* 2008

Clinical finding	Range of occurrence, %	References
Fever	98–100	[4, 13, 30–34]
Headache	41–90	[4, 13, 30–34]
Rash	20–80	[4, 13, 30–34]
Arthralgia	40–77	[4, 13, 30–34]
Hepatomegaly	24–29	[13, 30, 31, 33]
Cough	15–40	[4, 13, 30, 32–34]
Diarrhea	5–40	[4, 13, 30–34]
Splenomegaly	5–24	[13, 30, 31, 33]
Insect bite	0–39	[4, 30–34]
Nausea and/or vomiting	3–48	[4, 13, 30–34]
Abdominal pain	11–60	[4, 13, 30–32, 34]
Confusion	2–13	[4, 13, 30–34]

Tsioutis. *Acta Tropica* 2017

Acta Tropica 166 (2017) 16–24

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journal homepage: www.elsevier.com/locate/actatropica

Clinical and laboratory characteristics, epidemiology, and outcomes of murine typhus: A systematic review

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ABSTRACT

Murine or endemic typhus, a febrile disease caused by *Rickettsia typhi*, is often misdiagnosed due to its non-specific presentation. We sought to evaluate all available evidence in the literature regarding the clinical and laboratory manifestations, epidemiological characteristics, and outcomes of murine typhus.

Tsioutis. *Acta Tropica* 2017

Table 2
Clinical characteristics in studies of murine typhus.

Clinical characteristic*†	Adults and children	Children
Triad (fever, headache, rash)	184/525 (35.1%)	62/149 (41.6%)
Fever and headache	1009/1382 (73.0%)	101/190 (53.2%)
Fever and rash	740/1392 (53.2%)	130/275 (47.3%)
Headache	1237/1529 (80.9%)	101/190 (53.2%)
Malaise	601/894 (67.2%)	62/119 (52.1%)
Chills	656/1038 (62.6%)	44/92 (47.8%)
Myalgia	637/1234 (51.6%)	68/182 (37.4%)
Rash	884/1860 (47.5%)	130/275 (47.3%)
Anorexia	353/743 (47.5%)	83/161 (51.6%)
Back pain	43/123 (35.0%)	0
Non-productive cough	310/1154 (26.9%)	22/138 (15.9%)
Arthralgia	191/684 (27.9%)	30/130 (23.1%)
Nausea/vomiting	285/1069 (26.7%)	23/102 (22.5%)
Hepatomegaly	176/796 (22.1%)	37/221 (16.7%)
Conjunctivitis	94/518 (18.2%)	9/145 (6.2%)
Splenomegaly	139/828 (16.8%)	26/138 (18.8%)
Diarrhea	139/748 (18.6%)	50/182 (27.5%)
Abdominal pain	123/679 (18.1%)	41/147 (27.9%)
Sore throat	31/216 (14.4%)	20/95 (21.1%)
Lymphadenopathy	89/665 (13.4%)	31/278 (11.1%)
Photophobia	28/281 (10.0%)	8/81 (9.9%)
Complicated disease	459/1756 (26.1%)	42/275 (15.3%)

* The proportion of fever alone is not presented, as it was considered an inclusion criterion in most studies.

† For each clinical characteristic, the number of patients exhibiting the characteristic along with the total number of patients with available data are shown.

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Tsioutis. *Acta Tropica* 2017

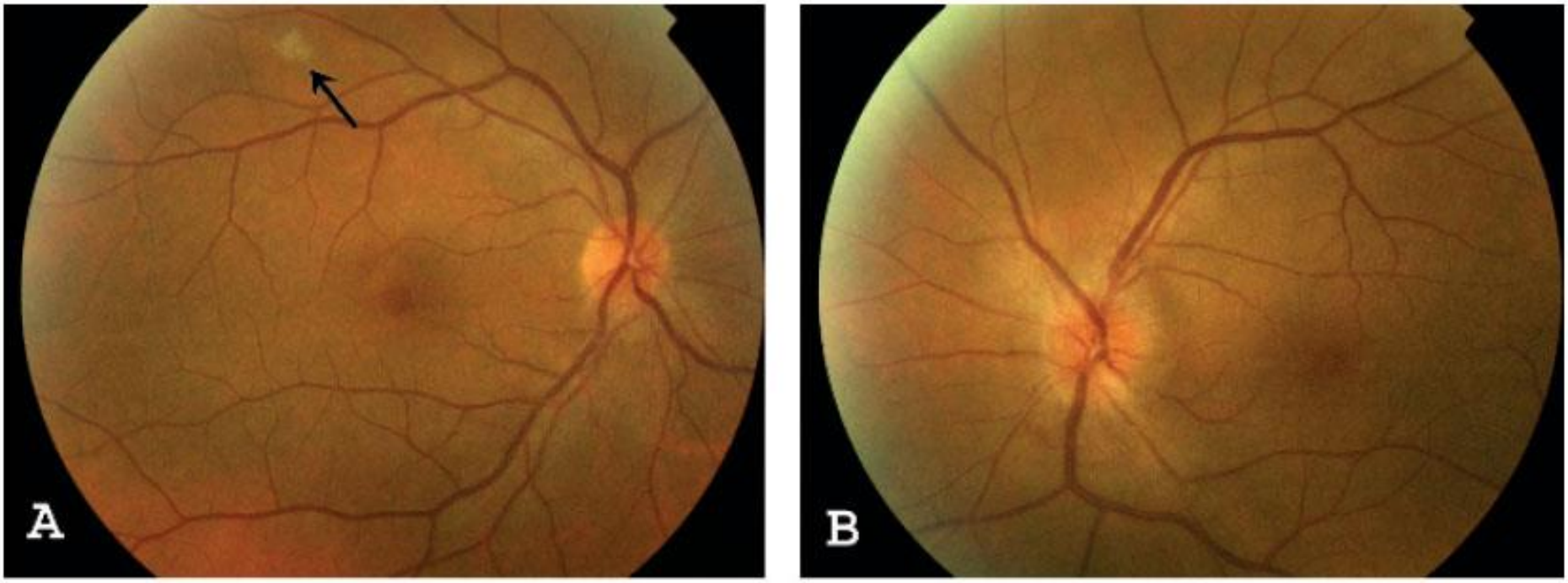
Tsioutis. *Acta Tropica* 2017

Table 3
Laboratory findings in studies of murine typhus.

Laboratory finding†	Overall	Children
Alanine and/or aspartate transaminase elevation	801/1014 (79.0%)	130/205 (63.4%)
LDH elevation	181/248 (72.9%)	59/96 (61.5%)
Hypoalbuminemia	181/301 (60.1%)	35/115 (30.4%)
High ESR	161/269 (59.9%)	41/63 (65.1%)
Thrombocytopenia	259/613 (42.2%)	67/221 (30.3%)
ALP elevation	142/349 (40.7%)	0
Anemia	240/631 (38.0%)	109/164 (66.5%)
Microscopic hematuria	101/270 (37.4%)	6/62 (9.7%)
Hyponatremia	147/426 (34.5%)	53/189 (28.1%)
Proteinuria	67/214 (31.3%)	7/62 (11.3%)
Creatine kinase elevation	34/118 (28.8%)	0
Leukopenia	167/694 (24.0%)	65/236 (27.5%)
Leukocytosis	114/620 (18.4%)	2/98 (2.0%)

† For each clinical characteristic, the number of patients exhibiting the characteristic along with the total number of patients with available data are shown.
LDH: lactate dehydrogenase; ALP: alkaline phosphatase.

Retinal lesions in murine typhus



8 of 9 patients (Tunisia) had bilateral optic involvement
Vitreous and/or retinal 3/8 symptomatic

Khairallah M *et al. Br J Ophthalmol* 2009; 93: 938–42

Deafness and rickettsia

Rocky Mountain SF common

Scrub typhus 1953 Noad & Haymaker

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

R. Premaratna,[1] T. G. A. N. Chandrasena,[2] A. S. Dassayake,[3] A. D. Loftis,[4] G. A. Dasch,[4] and H. J. de Silva[1]

Departments of [1]Medicine, [2]Parasitology, and [3]Pharmacology, Faculty of Medicine, University of Kelaniya, Sri Lanka, and [4]Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Premaratna R *et al; CID* 2006; 42:e6–8

Case 2

Dr Nick Beeching

LSTM

42 year old British teacher with a sore leg after travel to South Africa

Two week holiday with husband in South Africa

Fully immunised

Took Malarone

Visited towns & game parks

4 days after return sees family doctor with painful groin

Progress

Complaint:

"dullness in left thigh" -exquisitely tender lump left groin

GP diagnosis:

?? Incarcerated hernia

Referred to local hospital

Surgeons agree:

explore left groin

enlarged lymph nodes

Histology:

marked non-specific hyperplasia with suppurative granulomas

Progress

Sent home

Feels increasingly unwell
Headache
Fever
Lethargy and anorexia
Sore throat (? post anaesthesia)
Swollen painful left neck

2 days later (day 7 of illness) develops rash

Referred to Liverpool

Examination

Ambulant
Looks unwell

T 38.0ºC, BP 105/70 HR 80

Left neck node +

Chest & throat clear

Generalised rash

Further history

- Anaesthetist found lesion in hair
- Husband saw lesion under breast
- Patient found other lesions x 4

Results

Hb 14.5, Plt 185

WBC 3.4, Neut 1.6, Lymph 1.5

ESR 35

CRP 21

ALT 100 U/L (<40)

Other biochem normal

Diagnosis?

Outcome

- Clinical diagnosis
  African tick typhus
- Treated with doxycycline
- Better within 2 days
- Fully recovered
- Fame in women's magazine

Family Circle Aug 2006

'My holiday of a lifetime turned into a nightmare'

When Jayne Culshaw, 44, and her husband, Stephen, went on a safari, she came back with more than a tan...

For as long as I can remember, I'd wanted to visit South Africa. So it was a dream come true when, in March 2003, my husband, Stephen, and I decided we'd go on a safari holiday to the Kruger National Park. We had a really fabulous time, saw loads of lions, elephants, giraffes, rhinos and zebras, the game lodge was luxurious and the food was delicious – it was a wonderful trip.

The funny thing was that I remember saying to Stephen one day that I was a bit nervous about a lion getting in and attacking us. He said, 'It's not the big things I worry about, it's the little things!' What he meant was the insects.

A few days before the end of our stay, we went on a bush walk. We were advised to wear long trousers, socks and trainers, and to take a shower later in case any insects had got into our clothing. I did exactly as we were told. The walk was fun and I thought nothing more of it.

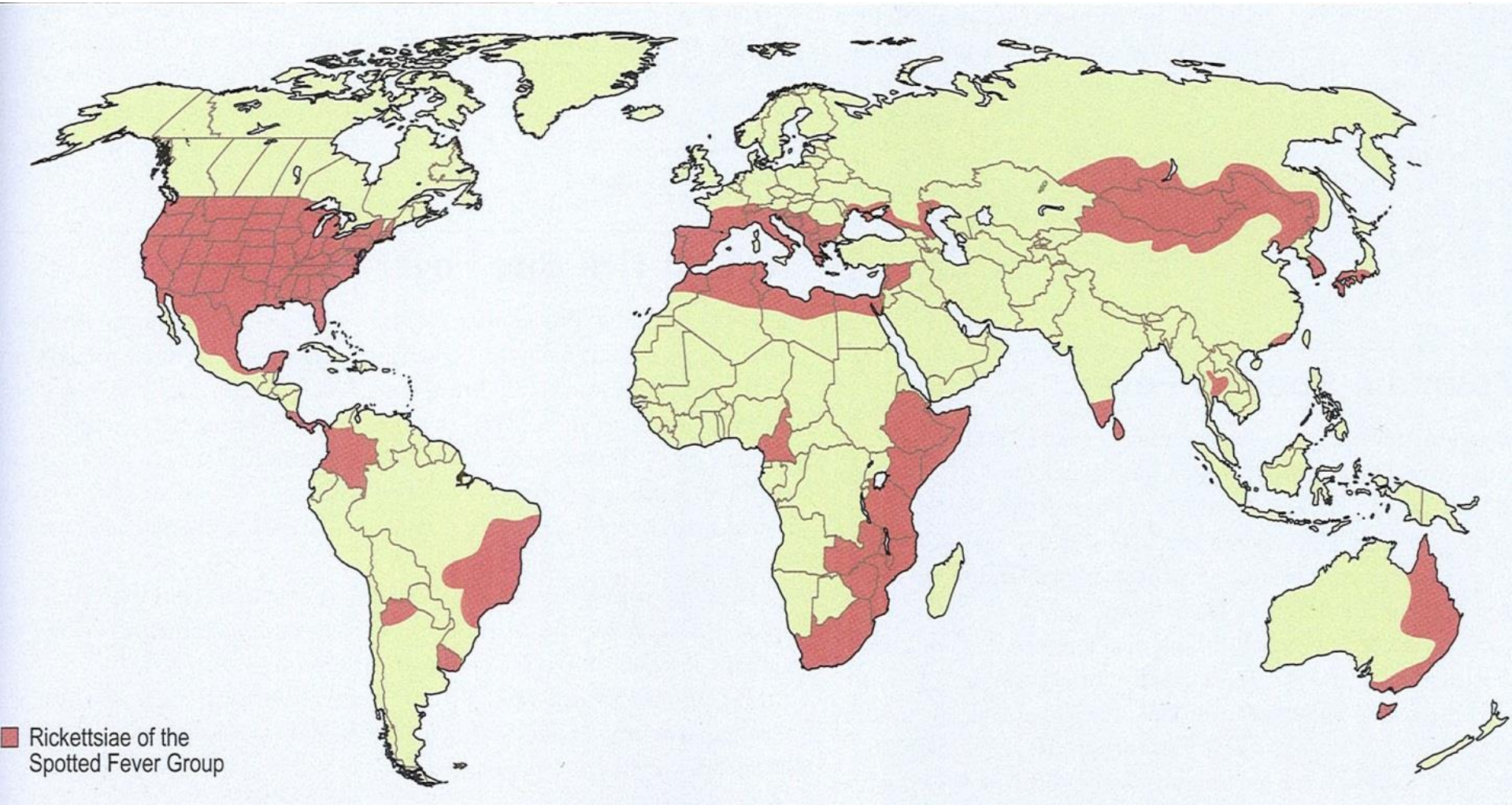
We came home on a weekend and I went back to work on Monday. I felt really tired the first day. I knew it wasn't jet lag – there's no real time difference between the UK and South Africa – so I thought it was just getting back into the old rhythm again.

Then a few days later I felt a dull ache in my groin. As I undressed that night, Stephen noticed a dark patch

What is tick typhus?

- **Tick typhus** is the name given to a collection of diseases caused by **rickettsia ticks**
- Infection is via a **bite** from an infected tick – in **Africa** the ticks are usually associated with **game animals**
- Symptoms include **fever**, **headaches**, **rash** and **swollen lymph glands**. Incubation is usually about a week
- African tick typhus is **rarely fatal** but, if untreated, symptoms can be **unpleasant** and **severe**, and could last **two weeks** or more. In other parts of the world tick typhus can be **life-threatening**

Spotted fever group



Sexton DJ, Walker DH. Ch49 in Guerrant RL *et al* *Tropical Infectious Diseases* 3rd ed. Elsevier 2011

Tick borne rickettsiae eg *R africae, R conorii*

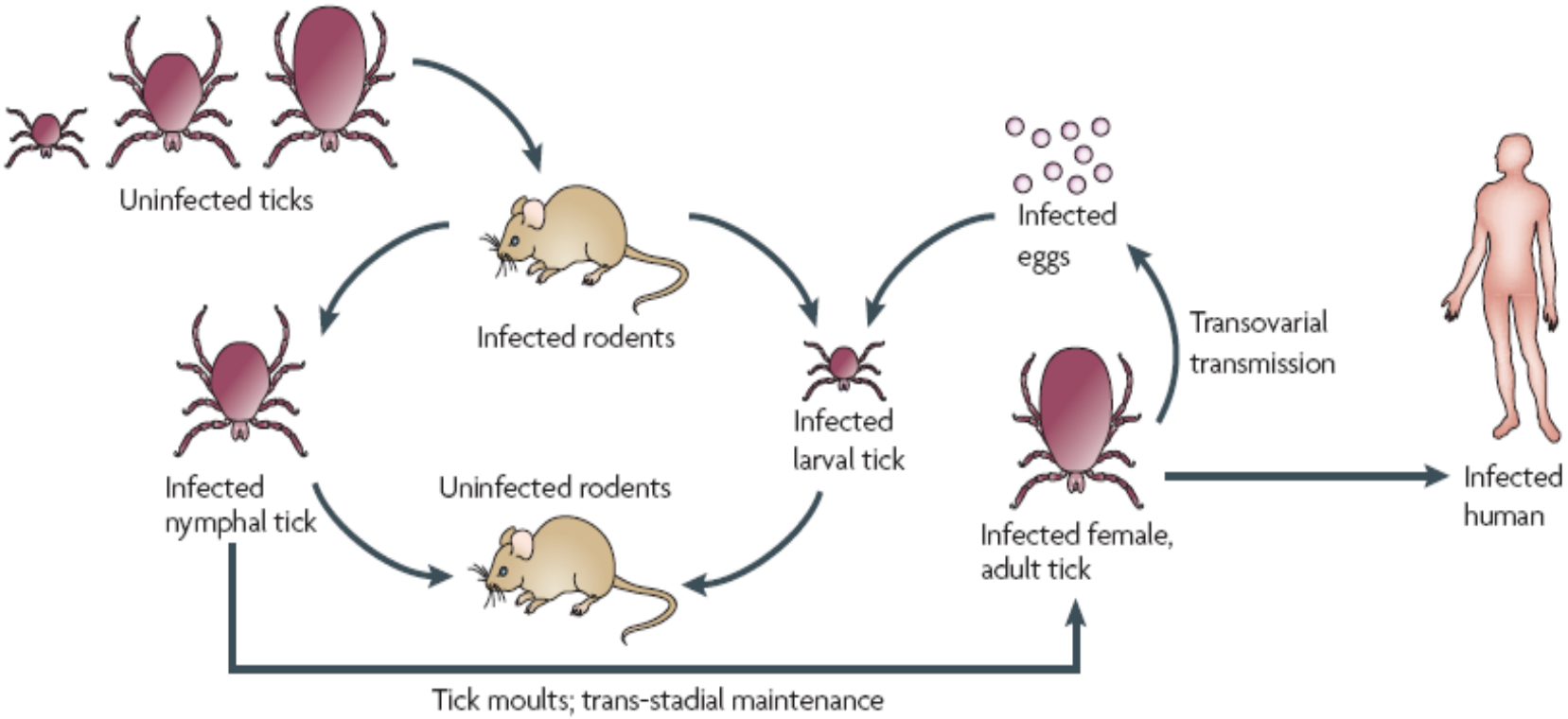


Figure 1 | **The life cycle of tick-borne rickettsiae.** Spotted-fever-group rickettsiae are maintained in nature by transovarial and trans-stadial transmission in ticks and horizontal transmission to uninfected ticks that feed on rickettsemic rodents and other animals.

Walker DH, Ismail N. *Nature Reviews* 2008

Clinical features: Tick typhus

Incubation period 2-14 days

Eschar (scalp,groin etc) may precede systemic symptoms

Similar syndrome to LBT

Generalised rash may be absent (*R. africae*)

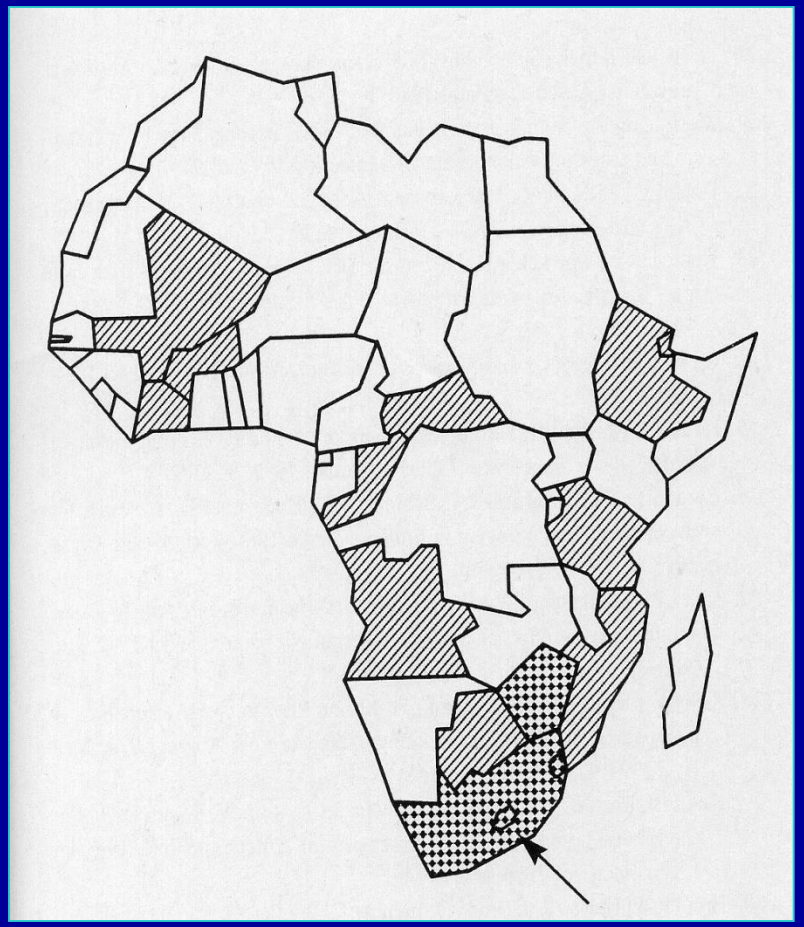
Mortality highest in RMSF (~7%)

Rickettsia africae in sport

8th "Raid Gauloise" multi-sport event in rural Lesotho & Natal 1997

13/331 French participants hospitalised

12 more symptomatic



Fournier PE *et al. Clin Infect Dis* 1998; 27: 316-23

Features

Tick bite noticed by 8/13 (61.5%)

Eschar	100%
Adenopathy	100%
Rash	15%

Hers

Eschar under bra strap

Rash on legs

Summary

- Consider African tick typhus in tourists with fever from Africa
- Symptoms non specific
- Headache often prominent
- Rash often absent
- Careful search for eschars eg hairline
- Lymph nodes
- Tick bites often not noticed
- Presumptive treatment with doxycycline

Jensenius M *et al. Clin Inf Dis* 2004; 39: 1493-9

Case 3

50 M Returned to UK ex S. Africa 26th Oct

- Presented 9th Nov.: Fever, confusion, rash
- History (from wife):
  - falls at home over the last 24hrs with head laceration
  - Rash – macular, non-itchy, torso then to arms/legs
  - Multiple insect/tick bites
- Heavy alcohol; smoker (cannabis + cigarettes)
- On examination:
  - T38.2, HR 120, BP 100/70. RR normal, chest clear, GCS 14
  - Unsteady gait, no other focal neurology
  - No meningism or photophobia
  - Macular erythematous rash all over body – sparing hands and face
  - Large eschar on ankle

Results

Thrombocytopenia (26; no fragments on film)
Mild lymphopenia (0.54)
Acute Kidney Injury (creatinine 280 from baseline 40)
Bilirubin normal; AST 288; GGT 155; INR 1.2
CRP 230; lactate 4.7.

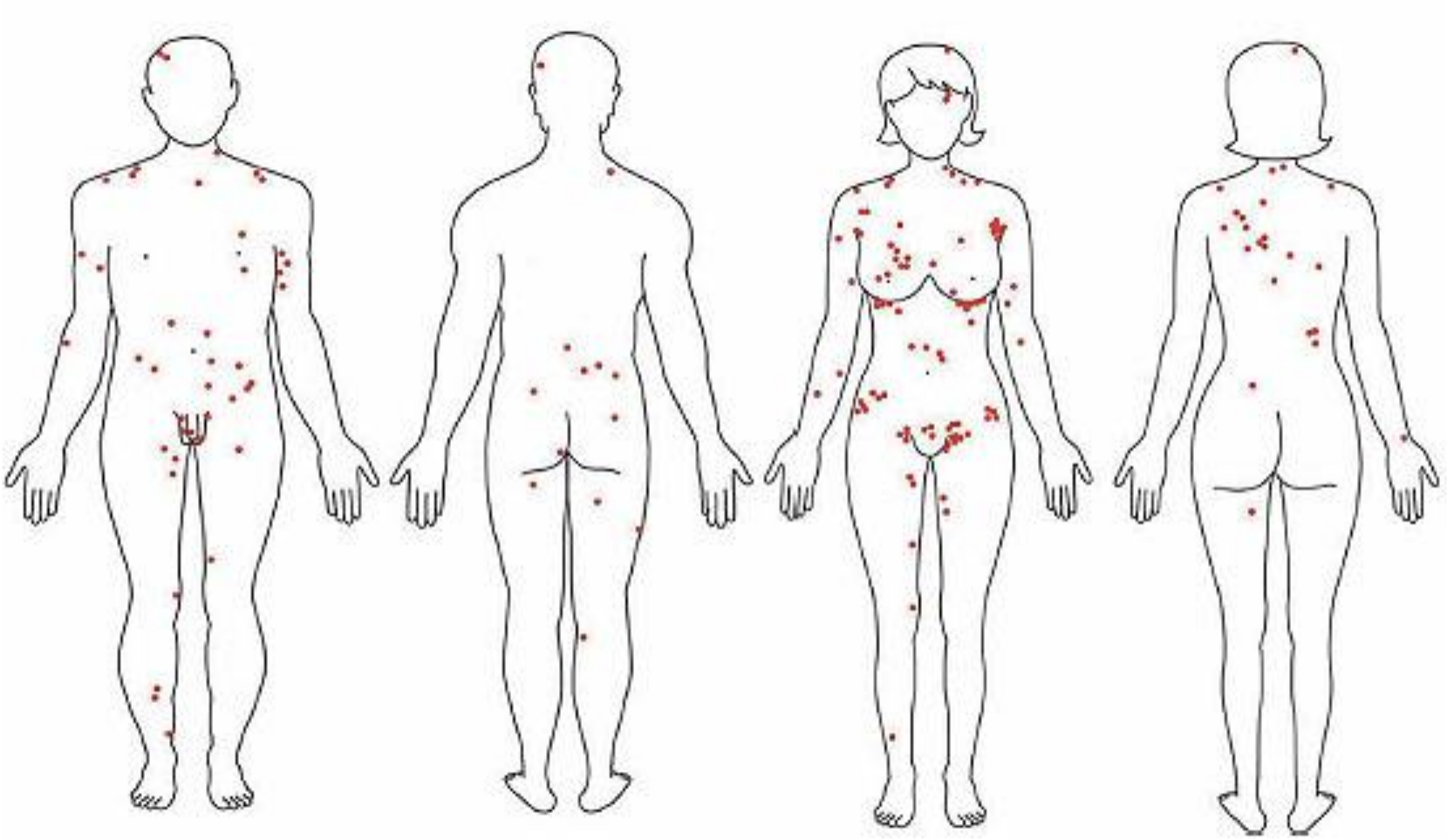
LP: WCC<5, normal protein/glucose/opening pressure.

HIV/syphilis/malaria negative
Blood Cultures ++ negative
Normal CTB/CXR.
USS liver: mild fatty change

Differentials

- CCHF to exclude
- Tick typhus
- Meningococcal infection
- Severe sepsis
- Leptospirosis
- East African trypanosomiasis
- Eschar – anthrax etc

Location of eschars in scrub typhus - Korea



268 patients - - most single eschar

Clue is adenopathy

Kim *et al* *AJT*MH 2006

Progress…

Rx

Ceftriaxone/aciclovir**/doxycycline** plus supportive

Positive (Urgent testing as CCHF in differential):

Rickettsial DNA blood (negative CSF; eschar not received)

Serology: **Spotted Fever Group: IgM negative; IgG positive**

Epidemic Typhus Group negative IgM/ IgG.

Increasing confusion Day 1 – but did not require ICU

Defervesced within 5 days of admission

Confusion resolved within 7 days

Discharged 2 weeks after admission back at baseline

Diagnosis

- *R conorii* infection (Mediterranean SF)
- Renal
- Lung
- Neurological

- Confirmed by blood PCR – rather later than might be expected

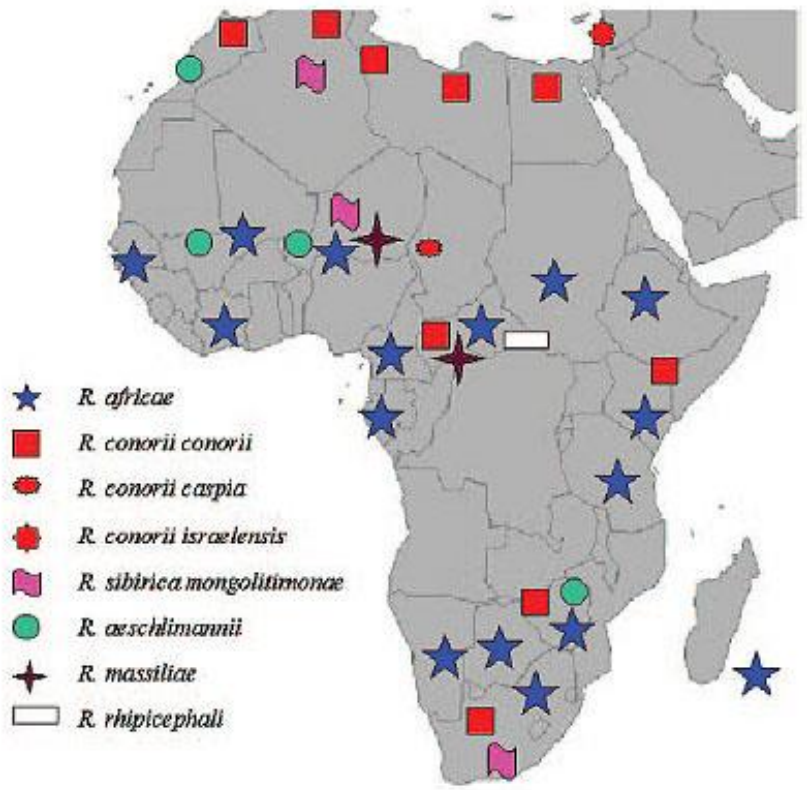


FIG. 7. Tick-borne rickettsiae in Africa. Colored symbols indicate pathogenic rickettsiae. White symbols indicate rickettsiae of possible pathogenicity and rickettsiae of unknown pathogenicity.

Parola P *et al*
***CMR* 2005; 18: 719-56**

Tick bite fever

	Mediterranean	Africa
Rickettsia	*R conorii*	*R africae*
Contact	Dogs	Rural
Affects tourists	Rare	Common
Fever	Yes	Yes
Rash	Common	Less
Eschar	Single	Multiple
Regional nodes	Yes	Common
Mortality	~2%	Rare

Case 4

72 F Retired nurse

Visited daughter & grandchildren Lusaka Zambia for 2 weeks

Goes every year

Dogs in household

Travel 5-20 Jan

Presented 28 Jan

Symptoms

Fatigue 7 days

Fever to 39 5 days

Vomiting, anorexia 4 days

Dry cough 1 day

Mild UTI symptoms 2 days

Rx co-amoxiclav from GP

Findings

T 37.6 P 94 BP 121/79 RR 16 Sats 95% on air GCS 15

No nodes or rash

Hb 147 WCC 9.3, N 8.4 L shift Lymph 0.6 Platelets 96

MPs negative CRP 276

Na 128 Bili 21 LFT normal Alb 34 U&E otherwise normal

US liver normal

MSU probable *E coli* UTI

CXR clear

Echocardiogram moderate/severe mixed aortic stenosis/regurgitation

Progress

Diagnosis wide

Rx Coamoxiclav, gentamicin

Then tazocin/clarithromycin

Swinging fever to 40, hypotension to 79/53, MEWS to 10

Increased resp rate and low Sats; malaena x 1

Hb dropped from 145 to 105, albumin to 22, lactate 3

Rash on day 7 of admission (day 12 of illness)

Macular rash including palms and soles (non blanching)

No eschar

Laboratory report

FINAL REPORT

Flavivirus Results	
Dengue virus RNA	Negative
Alphavirus Results	
Chikungunya virus RNA	Negative
Rickettsia Results	
Spotted Fever Group IgM (IFA)	Negative
Spotted Fever Group IgG (IFA)	Negative
Epidemic Typhus Group IgM (IFA)	Negative
Epidemic Typhus Group IgG (IFA)	Negative
Rickettsia spp. DNA (*GltA* target)	POSITIVE
***Coxiella burnetii* Results**	
Coxiella burnetii PCR	Negative
***Coxiella burnetii* Comment**	These PCR results are based upon a developmental assay. Full characterisation and validation of this assay is on going.

02 MAR 2017

Date reported: 29.02.2016 16:39
Date printed: 01.03.2017 15:34

Laboratory report

FINAL REPORT

Flavivirus Results	
Dengue virus RNA	Negative
Alphavirus Results	
Chikungunya virus RNA	Negative
Rickettsia Results	
Spotted Fever Group IgM (IFA)	Negative
Spotted Fever Group IgG (IFA)	Negative
Epidemic Typhus Group IgM (IFA)	Negative
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02 MAR 2017

Date reported: 29.02.2016 16:39
Date printed: 01.03.2017 15:34

Code:	Panel:		Status:	Other:
	DNR	0	Reported	

WRD: C:10/02/2016 ***** R:10/02/2016

--START OF REPORT--

Reference report from PHE Laboratory Porton Down:

Specimen Type Plasma EDTA.

Rickettsia Results

Spotted Fever Group IgM (IFA)	POSITIVE
Spotted Fever Group IgG (IFA)	POSITIVE
Epidemic Typhus Group IgM (IFA)	POSITIVE
Epidemic Typhus Group IgG (IFA)	POSITIVE

Report Comment:
Seroconversion since the previous sample dated 29 January.
The titres for antibodies to spotted fever group rickettsiae are higher than those for epidemic typhus group (spotted fever group IgM 1:128, IgG > 1:2048).
This is likely to represent African tick typhus.

Consider doxycycline treatment if the patient is still unwell.
(Note that doxycycline is contraindicated in pregnancy other than for treatment of life-threatening infection. If the pregnant patient is acutely unwell, please phone to discuss.)

***Leptospira spp.* Results**

Leptospira Lip32 DNA	Negative
Leptospira 16S DNA	Negative

Report comment:
NOTE THAT THIS IS A FINAL REPORT, PROVIDING THE RICKETTSIAL SEQUENCING RESULTS, ON A SAMPLE TAKEN IN FEBRUARY 2016.

Rickettsia Sequencing result (OmpB target): Groups with R.conorii and Israeli tick typhus strains.
Note subsequent seroconversion to rickettsial antibodies in another sample (undated, but received in our lab on 12 February 2016).

No serological or molecular evidence of Coxiella infection.

Results dependent upon clinical history, onset date and occupational history.

Antibodies to C. burnetii are detectable by 7-15 days post-onset, and are present in 90% of patients by 3 weeks in acute Q-fever.

Please send a repeat sample if still clinically relevant.

Finally

SF group seroconversion (negative initially) > endemic typhus group seroconversion

Positive PCR in blood for *R conorii*

Doxycycline added

Did well

The problem with serology….

Table. Kinetics of species-specific antibody titers in patient infected with *Rickettsia honei*, Nepal, 2009*

Species tested	IgG/IgM titer by date			
	Apr 20	Apr 24	Apr 29	May 15
R. honei	Neg	256/32	512/32	1,024/64
R. felis	32/0	256/16	256/16	256/16
R. massiliae	Neg	Neg	Neg	128/16
R. aeschlimannii	Neg	Neg	Neg	128/16
R. conorii subsp. *israelensis*	Neg	Neg	Neg	128/16
R. conorii subsp. *conorii*	Neg	Neg	Neg	128/16
R. conorii subsp. *mongolitimonae*	Neg	Neg	Neg	128/18
R. slovaca	Neg	Neg	Neg	128/16
R. helijongangensis	Neg	32/32	64/32	64/64
R. AT1	Neg	32/32	64/32	64/64
R. africae	Neg	32/32	64/32	64/64
R. japonica	Neg	32/32	64/32	64/64
R. conorii subsp. *indica*	Neg	Neg	64/32	64/32
R. typhi	Neg	Neg	Neg	64/64
R. prowazekii	Neg	Neg	Neg	64/64
Orientia tsutsugamushi serotype Kawasaki	Neg	Neg	Neg	64/64
O. tsutsugamushi serotype Gilliam	Neg	Neg	Neg	Neg

*Ig, immunoglobulin; neg, negative. Titer cutoff values were ≥128 for IgG and ≥64 for IgM. A negative titer was reported when an initial serum screening result was negative. A titer of 0 was reported when an initial screening result was positive but no Ig was detected.

Numerous cross reactions (Marseilles lab) (*R honei* case)

Effects of Antibiotic Treatment on the Results of Nested PCRs for Scrub Typhus[▽]

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In order to determine the effects of antibiotic treatment on the results of nested PCRs for scrub typhus, we investigated the frequency of positive outcomes at various times after antibiotic administration in patients with scrub typhus. The rate of detection by nested PCR with blood buffy coat before antibiotic administration was 90.5%. However, this decreased to 60.5% within 3 days after administration of antibiotics such as doxycycline and rifampin and to 10% by the fourth day following antibiotic administration. Since the sensitivity of nested PCR can be affected by antibiotic administration, clinicians should perform this PCR before antibiotic administration and at the latest within 3 days after antibiotic administration.

PCR in buffy coat v sensitive (compared to IFA serology)

- 90% before treatment
- 60% after 3 days Rx
- 10% after 4 days Rx

Eschars better

Similar results reported for SFG (correlates but better than culture)

Angelakis *et al PLoS NTD* 2012; 6(3): e1540

REVIEW

COID 2016

CURRENT OPINION

State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus

Daniel H. Paris[a] *and J. Stephen Dumler*[b]

Purpose of review

With improved malaria control, acute undifferentiated febrile illness studies in tropical regions reveal a startling proportion of rickettsial illnesses, especially scrub typhus, murine typhus, and spotted fever group rickettsioses. Laboratory diagnosis of these infections evolved little over the past 40 years, but combinations of technologies like PCR and loop-mediated isothermal amplification, with refined rapid diagnostic tests and/or ELISA, are promising for guidance for early antirickettsial treatment.

Recent findings

The long-term reliance on serological tests – useful only late in rickettsial infections – has led to underdiagnosis, inappropriate therapies, and undocumented morbidity and mortality. Recent approaches

Table 1. Median clinical sensitivity of PCR methods for detection of spotted fever group and typhus group rickettsia in blood and skin/eschar biopsy samples[a]

Sample	*Rickettsia*	Method	Percentage clinical sensitivity		
			Number of assays	Median (IQR)	References
All	PanRick	All	145	23 (15–34)	[43▪,44,54]
	SFGR		331	48 (34–65)	[53,54]
	TGR		257	5 (3–7)	[43▪,44]
Skin	All	All	233	43 (7–55)	[43▪,54]
	SFGR		101	67 (55–79)	
	TGR		88	6 (5–6)	
Blood	All	All	331	18 (4–30)	[43▪,44]
	PanRick		101	18 (12–23)	
	SFGR		230	42 (24–56)	
	TGR		169	3 (2–10)	
All	PanRick	Real-time PCR	525	7 (4–23)	[43▪,44]
	SFGR	Real-time PCR	123	23 (14–33)	
	TGR	Real-time PCR	257	5 (3–7)	
	SFGR	Nested PCR	29	31 (31–31)	[53]
	SFGR	Conventional PCR	179	69 (61–80)	[53,54]

[a]Derived from studies for which serologic and PCR results on more than 10 patients were reported since 2013 identified using search terms 'rickettsia', 'spotted fever', 'typhus' and 'PCR', 'real-time PCR', 'nested-PCR', 'qPCR', 'quantitative PCR'. PanRick – assays that target the genus *Rickettsia*; SFGR – assays that target spotted fever group rickettsiae; TGR – assays that target typhus group rickettsiae. Number of assays column includes total assays reported, including some on the same samples but different approaches or targets. IQR, interquartile range.

Table 2. Sensitivity and specificity of serological tests for confirmation of scrub typhus, spotted fever rickettsiosis, and murine typhus

Disease	Serological assay	Sensitivity (%)	Specificity (%)	References
Scrub typhus	IFA IgG	91	96	[60]
	IFA IgM	70–87	84–100	[16,17▪▪,60]
	ELISA IgG	80–97	89–98	[60–63]
	ELISA IgM	84–100	73–99	[60,64]
	ImmChrom IgG RDT	86–95	96–100	[38,60,65]
	ImmChrom IgM RDT	82–94	86–100	[35,38,40,60,65]
	Dot EIA	60–100	94–99	[36,60,66]
Spotted fever rickettsiosis	IFA IgG	85–100	99–100	[67–69]
	IFA IgM	83–85	100	[68,69]
	ELISA IgG	83	87	[68,70]
	ELISA IgM	98	94[a]	[68]
Murine typhus	IFA IgG	≥83	≥93	[67]
	IFA IgM	53–85	99	

[a]Increasing data suggest lower specificity [56,59,68].
IFA, immunofluorescence assay; ImmChrom, immunochromatographic; RDT, rapid diagnostic test.

Treatment

Doxycycline 200 mg stat dose in epidemic situations of LBT

200 mg x2 effective in MSF

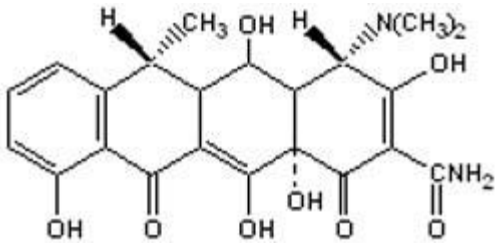
Otherwise at least 5 days for severe cases and in RMSF

Chloramphenicol 500 mg 6 hrly for 7 days an alternative

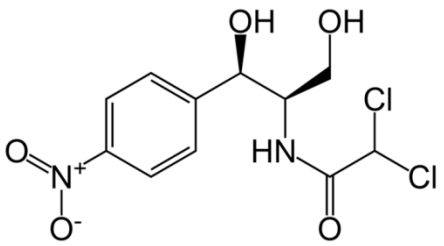
Ciprofloxacin may not perform as well in vivo as MICs suggest

Single dose azithromycin

Rifampicin in areas where TetR



Doxycycline



Chloramphenicol

Scrub typhus - Cochrane review

Data are limited because trials are small

There are no obvious differences between tetracycline, doxycycline, telithromycin,or azithromycin

Rifampicin may be better than tetracycline in areas where scrub typhus appears to respond poorly to standard anti-rickettsial drugs

Liu Q, Panpanich R. Antibiotics for treating scrub typhus. *Cochrane Database Syst Rev* 2002, Issue 3: Art. No CD002150. DOI: 10.1002/14651858.CD002150 (recertified 2010)

Diagnosis & management

- History of tick exposure - ??
- Clinical - non specific symptoms
- Serology - only positive after 7-10 days
- Biochem/haem - non specific:

  ↑acute phase, ↓Hb, ↓plt, WBC normal

  ↑LFT, ↑LDH, ↑CK
- Culture - feasible, but not readily available
- Immunohistology/PCR of skin biopsy (rash, eschar) or EDTA blood
- Treat on suspicion - doxycycline

Epidemiological

- The range of each rickettsiosis is increasing
- Known species are being found in other hosts/vectors including man
- More species are being defined
- The group has potential for deliberate release

- Consider rickettsial aetiology in patients in or returning from an endemic country and presenting with fever and
    - lymphadenopathy/hepatosplenomegaly
    - rash (discrete maculo-papular)
    - delayed onset pneumonitis, myocarditis, tinnitus, deafness, retinitis, encephalitis
    - late onset arthritis and erythema nodosum
    - pancytopenia/bicytopenia
- Rash may involve palms
- Look for eschar (clue lymphadenopathy)
- Careful interpretation of serology if patient is from an endemic setting

Diagnosis & management

- Sero-diagnosis is improved by molecular techniques
- Therapeutic trial with doxycycline justified in resource poor settings
- Antibiotic resistance is already an issue with scrub typhus
- Prospective trials are needed for fluoroquinolones, azithromycin etc

Typhus is not dead. It will live on for centuries and it will continue to break into the open whenever human stupidity and brutality give it a chance, as most likely they occasionally will.

Hans Zinsser, *Rats Lice and History* 1934