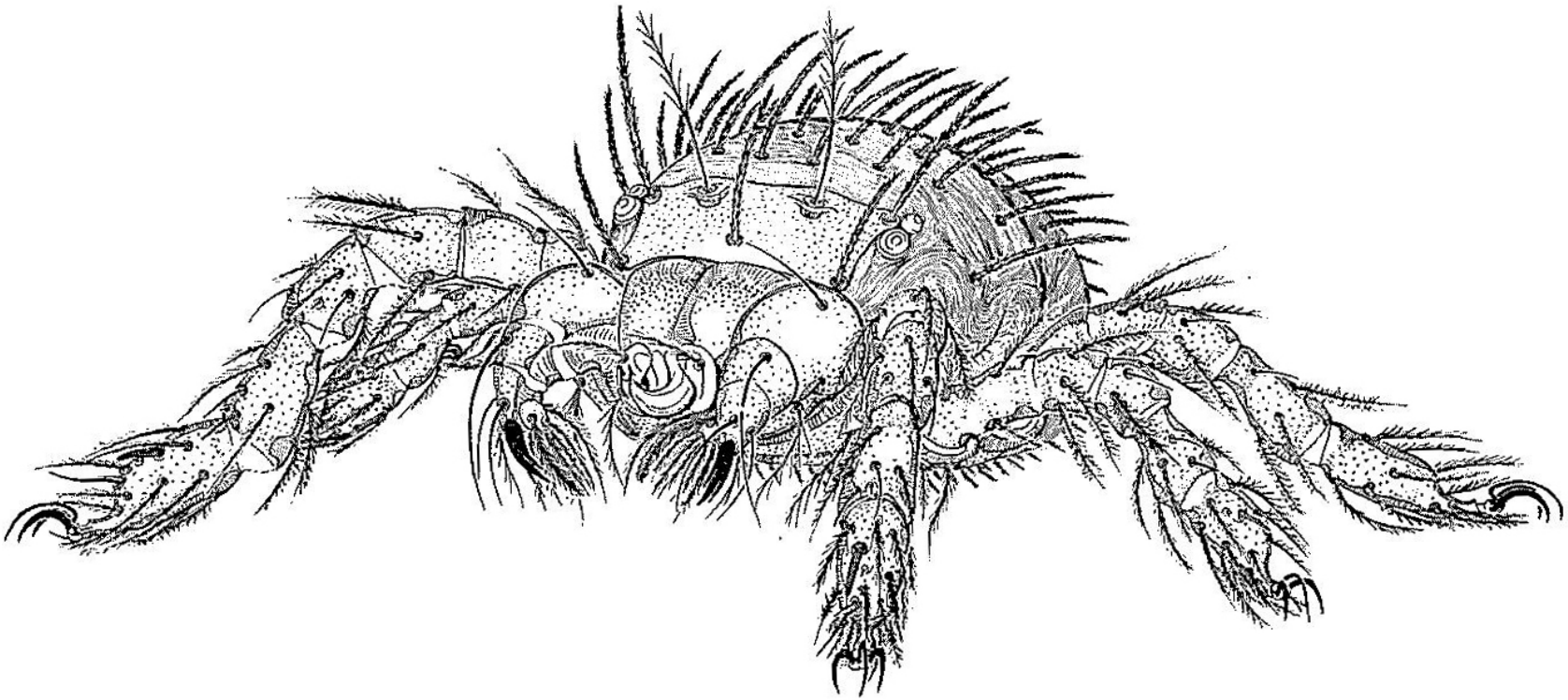
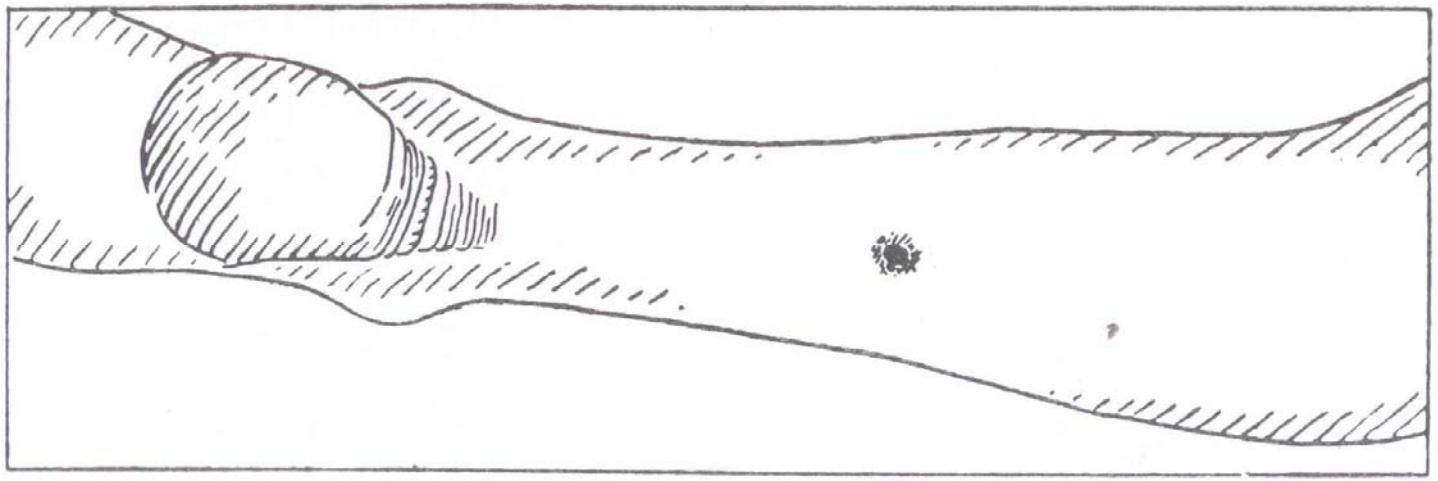
Scrub Typhus: current standing and future challenges



Nick Day

Scrub typhus

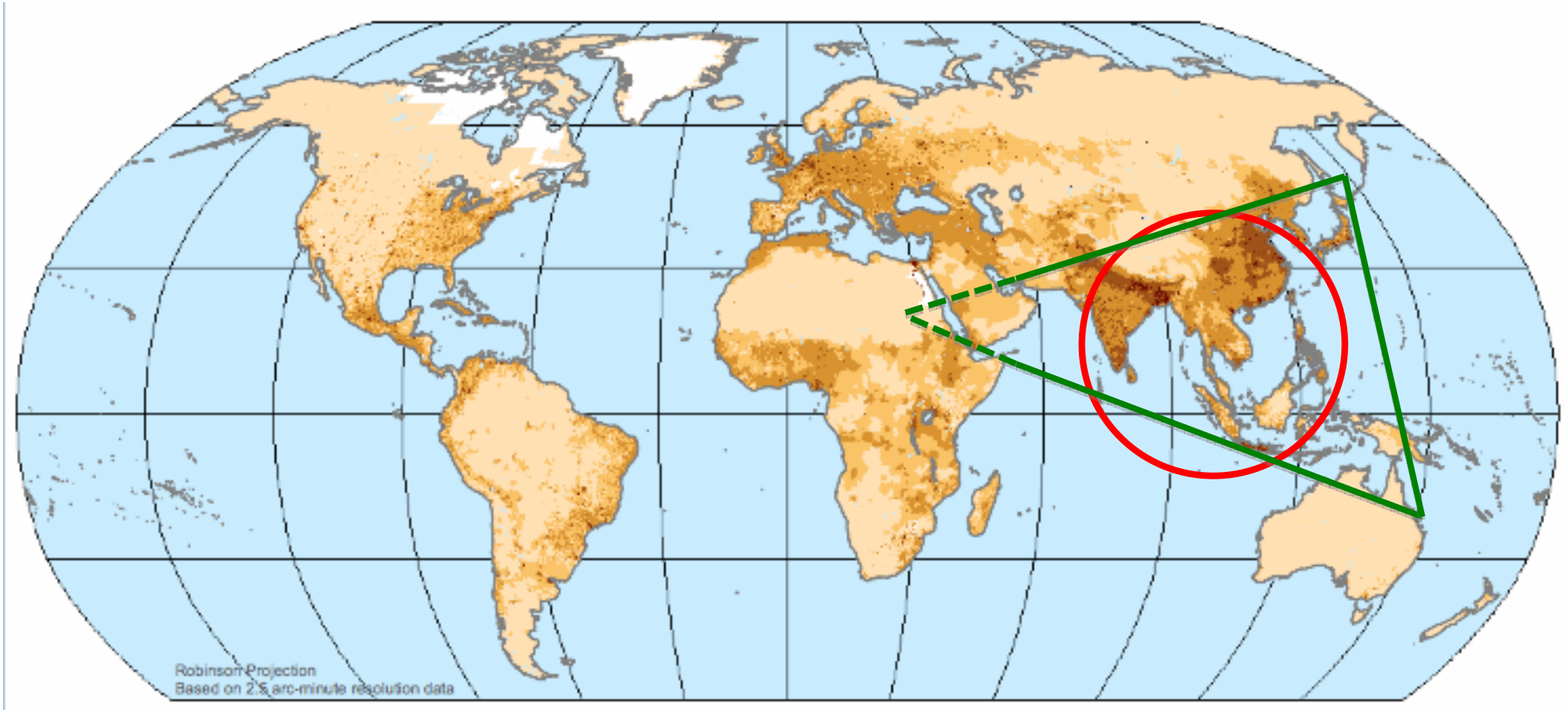


- More than one billion people exposed
- One million cases per year

"Scrub typhus is probably the major cause of undiagnosed treatable disease"

World Health Organization, 1999

The scrub typhus triangle…



Half of the world's population within 2000 miles of Bangkok

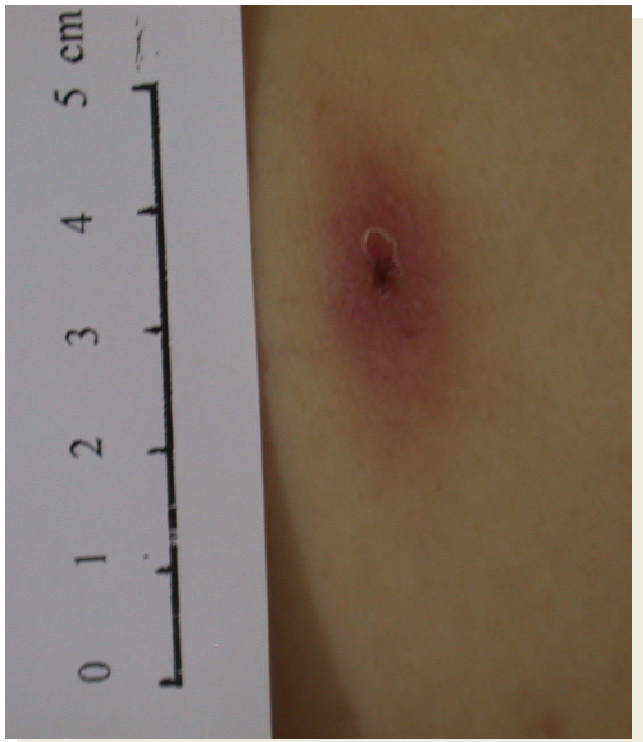
Orientia tsutsugamushi

- Tsutsugamushi = ‘poisonous worm’ or ‘wild beast’
- Transmitted by larval Leptotrombidium mites
- Rodent intermediate hosts

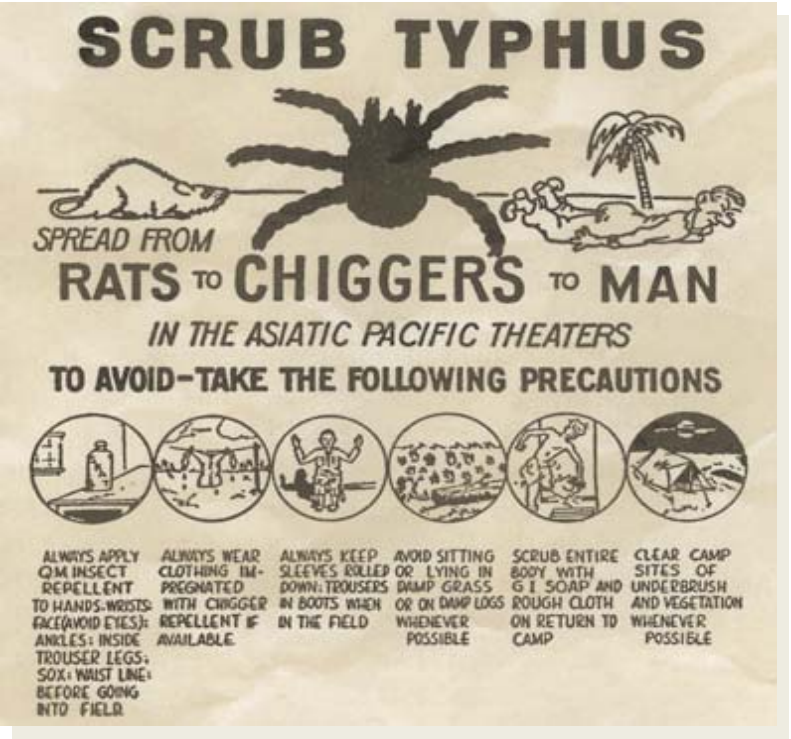
103. Scrub Typhus Research Unit. Routine examination of a day's collection of mammal hosts.

Scrub typhus - Clinical features

- 6-18 day incubation period
- Eschar in ~ 50%
- Regional lymphadenopathy
- Fever, headache, myalgia
- Hearing loss
- Maculopapular rash
- Conjunctival suffusion
- Cough
- Apathy, stupor, convulsions, coma



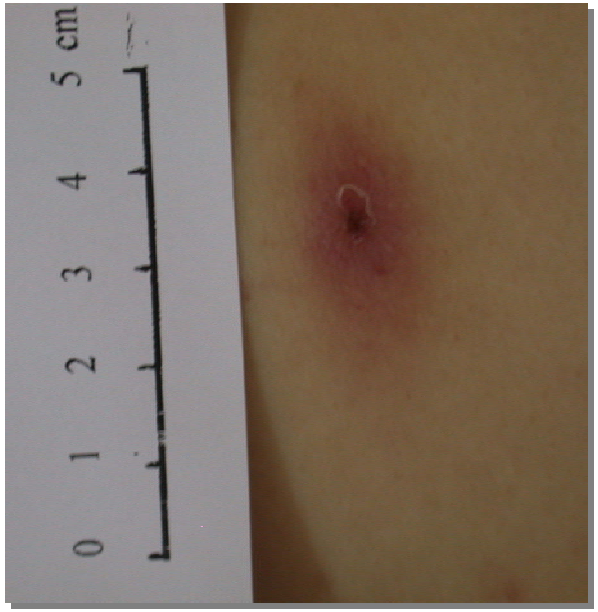
World War II



- More morbidity and mortality than from malaria
- More casualties due to scrub typhus (>10,000) than to direct war casualties
- Reported case fatality ranged from 1.5% (Ceylon) to 35.3% (Finchhaven, New Guinea)

Scrub typhus - challenges

- Clinical epidemiology - underrecognised
- Diagnostics
- Treatment
- Pathobiology & pathophysiology
- Vaccines and prevention



Mahosot Hospital, Vientiane, Laos

Blood culture, malaria smear negative fever in adults over 2 years (n = 427)

Scrub typhus	63 (15%)
Leptospirosis	43 (10%)
Dengue	43 (10%)
Murine typhus	41 (10%)
Spotted fever	11 (3%)
Japanese Encephalitis Virus	10 (3%)
Typhus total	28 %

Doxycycline-responsive pathogens 38%

Scrub typhus is a major cause of fever in Thailand

Study A - Acute febrile illness (Suttinont et al., 2006)

- Thailand - 5 community-based hospitals - 845 patients
- 19.9% of patients had scrub typhus infections (second highest cause of fever)

Study B - Acute febrile illness (Leelarasamee et al., 2004)

- Thailand - 10 community-based hospitals - 1240 patients > 2 years old
- 7.5% of patients had scrub typhus infections (highest cause of fever)

OPEN ACCESS Freely available online

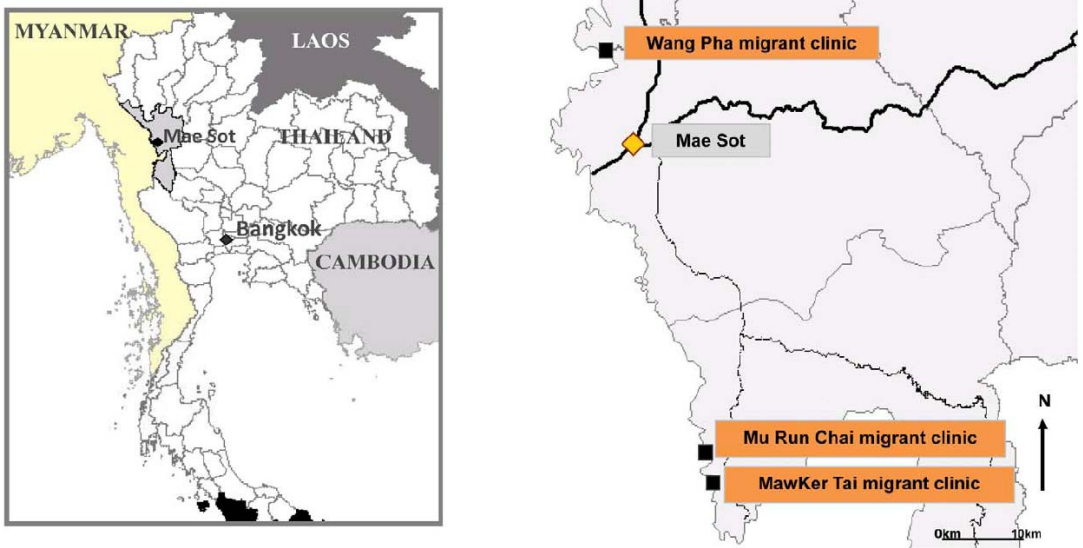
PLoS NEGLECTED TROPICAL DISEASES

Arthropod Borne Disease: The Leading Cause of Fever in Pregnancy on the Thai-Burmese Border

Rose McGready[1,2,3]*, Elizabeth A. Ashley[1,4], Vanaporn Wuthiekanun[2,3], Saw Oo Tan[1], Mupawjay Pimanpanarak[1], Samuel Jacher Viladpai-nguen[1], Wilarat Jesadapanpong[2], Stuart D. Blacksell[2,3], Sharon J. Peacock[2,5], Daniel H. Paris[2,3], Nicholas P. Day[2,3], Pratap Singhasivanon[2], Nicholas J. White[2,3], François Nosten[1,2,3]

1 Shoklo Malaria Research Unit (SMRU), Mae Sot, Tak, Thailand, **2** Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand, **3** Centre for Tropical Medicine, Churchill Hospital, Oxford, United Kingdom, **4** Imperial College NHS Trust, London, United Kingdom, **5** Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom

PLoSNTD 2010;4:e888



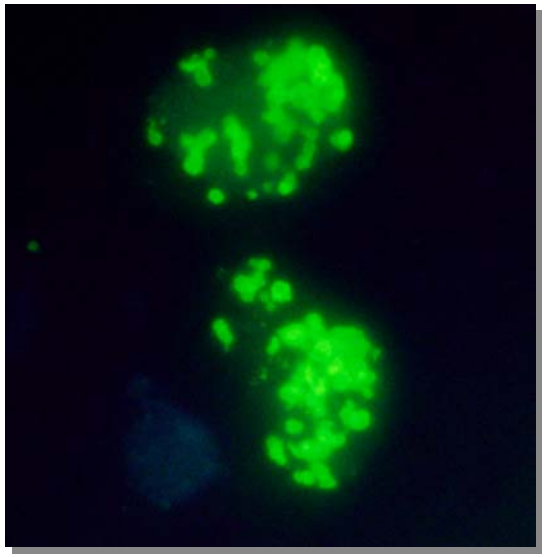
Malaria	24.2%
Pyelonephritis	19.4%
Rickettsia	12.3%
Dengue	9.5%
ARI	8.1%
Leptospirosis	2.4%

Rickettsioses in Asia - challenges

- Clinical epidemiology
- Diagnostics
  - Overall poor in tropical rickettsiology
  - Need gold standard, POC & epidemiological tests
  - Microbiology labs inadequate in quantity & quality
  - Little or no QA/QC
- Treatment
- Pathobiology & pathophysiology
- Vaccines and prevention

Current rickettsial diagnosis

- *In vitro* isolation
  - High specificity, Low sensitivity
  - Slow (weeks)
  - Requires biocontainment lab
- Serology
  - Many formats available (which tests to use?)
  - Inaccurate with single acute phase sample
- Molecular/genetic
  - Many varieties under development
  - Expensive
- Antigen
  - None available



Scrub Typhus Serologic Testing with the Indirect Immunofluorescence Method as a Diagnostic Gold Standard: A Lack of Consensus Leads to a Lot of Confusion

Stuart D. Blacksell,[1,2] Naomi J. Bryant,[3] Daniel H. Paris,[1] Jenny A. Doust,[4] Yoshihiro Sakoda,[5] and Nicholas P. J. Day[1,2]

[1]Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [2]Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Churchill Hospital, University of Oxford, and [3]London School of Hygiene and Tropical Medicine, London, United Kingdom; [4]Centre for General Practice, School of Medicine, University of Queensland, Herston, Queensland, Australia; and [5]Graduate School of Veterinary Medicine, University of Hokkaido, Sapporo, Japan

Blacksell et al (2007) *Clin Inf Dis, 44, 391 - 40.*

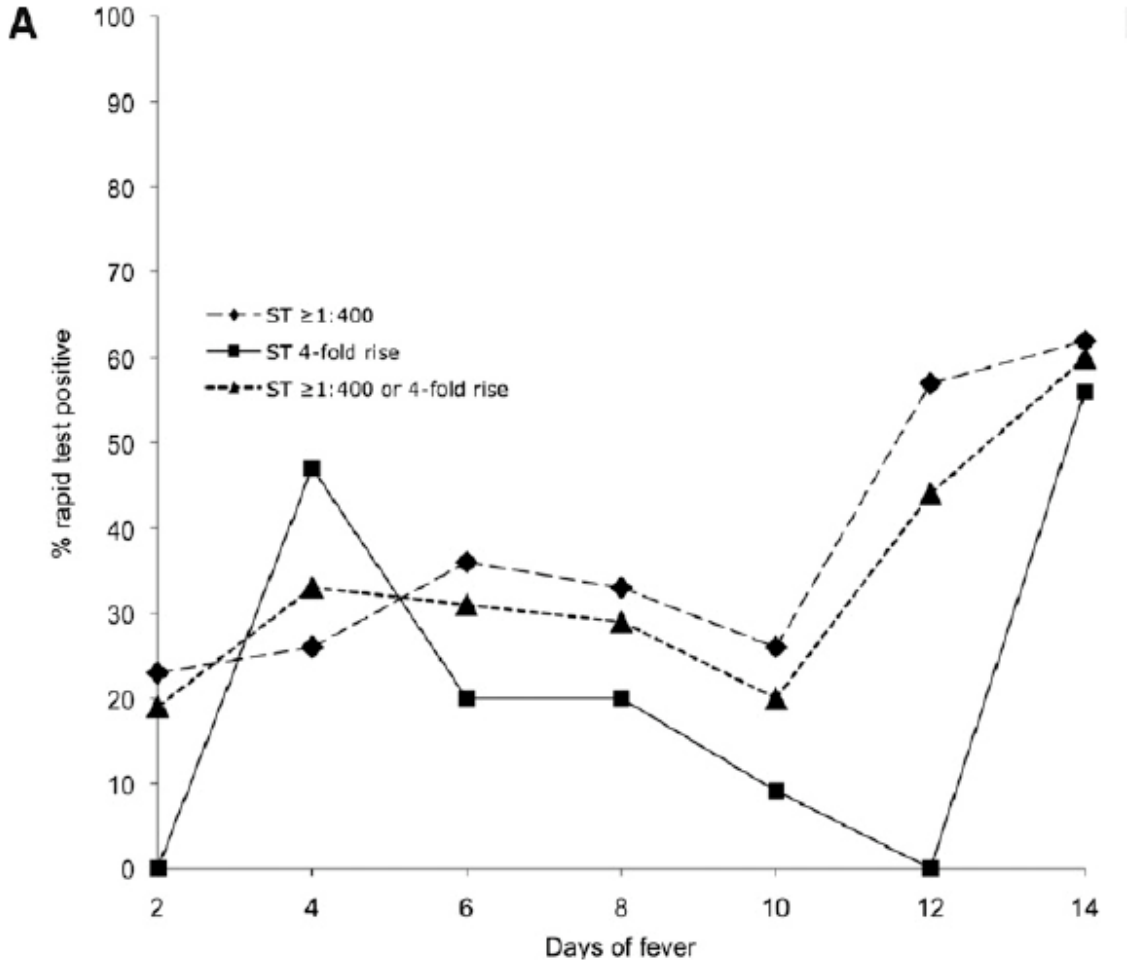
- 123 studies analysed.
- No consensus on antigens used
- No consensus on cutoffs/criteria and little evidence supporting those used

- Need for non-serological, inexpensive diagnostic tests
- Need for external quality assurance scheme for IFA and any new standardised tests

Accuracy of Rapid IgM-Based Immunochromatographic and Immunoblot Assays for Diagnosis of Acute Scrub Typhus and Murine Typhus Infections in Laos

Stuart D. Blacksell,* Kemajittra Jenjaroen, Rattanaphone Phetsouvanh, Ampai Tanganuchitcharnchai, Phonlavanh Phouminh, Simalee Phongmany, Nicholas P. J. Day, and Paul N. Newton

Wellcome Trust-Mahosot Hospital-Oxford Tropical Medicine Research Collaboration, Microbiology Laboratory, Mahosot Hospital, Vientiane, Laos; Centre for Tropical Medicine, University of Oxford, Churchill Hospital, Oxford, United Kingdom; Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand



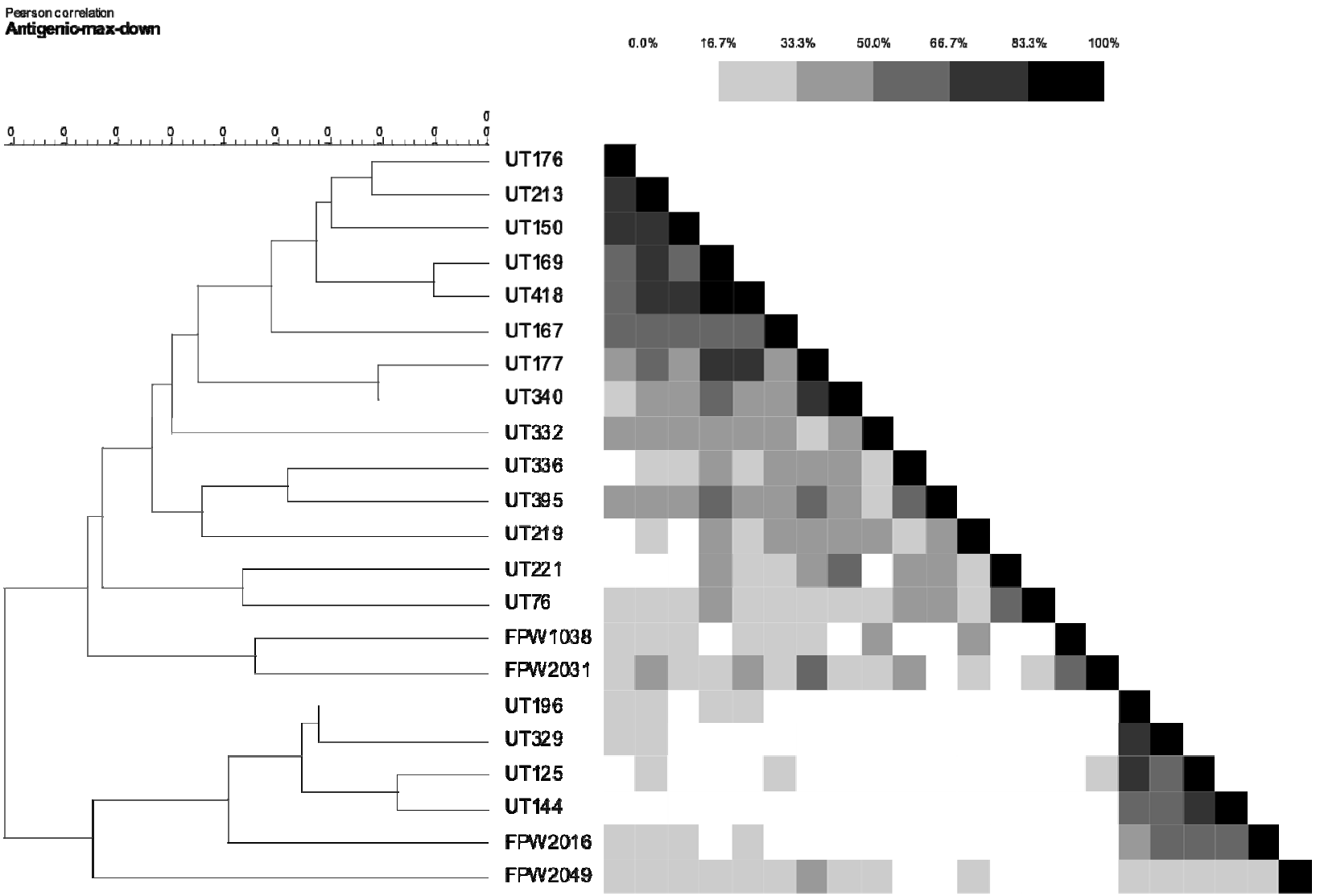
AJTMH 2010;83:365

ICT Sensitivity 23.8%
ICT Specificity 86.2%

101/1,030 had ST

Antigenic relationships

IFA cross binding



IFAs based on heterologous strains can work very poorly…

Comparison of Conventional, Nested, and Real-time Quantitative PCR for the Diagnosis of Scrub Typhus

Dong Min Kim, Geon Park, Hyong Sun Kim, Joo Young Lee, Ganesh Prasad Neupane, Stephen Graves, and John Stenos*

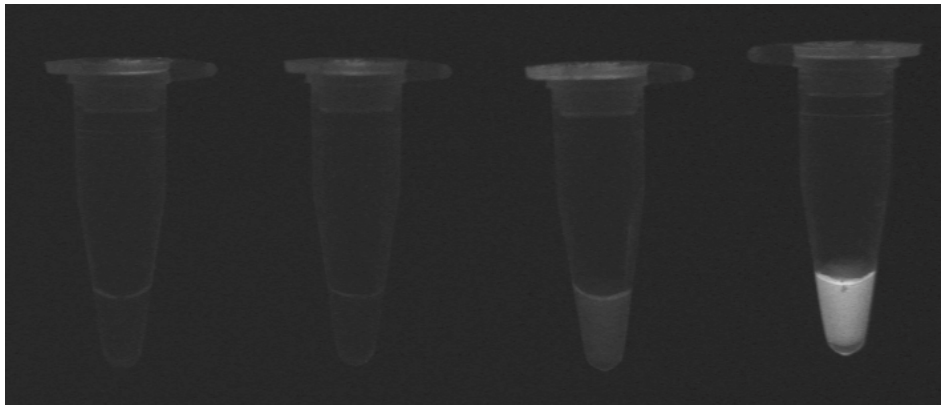
JCM Online before print

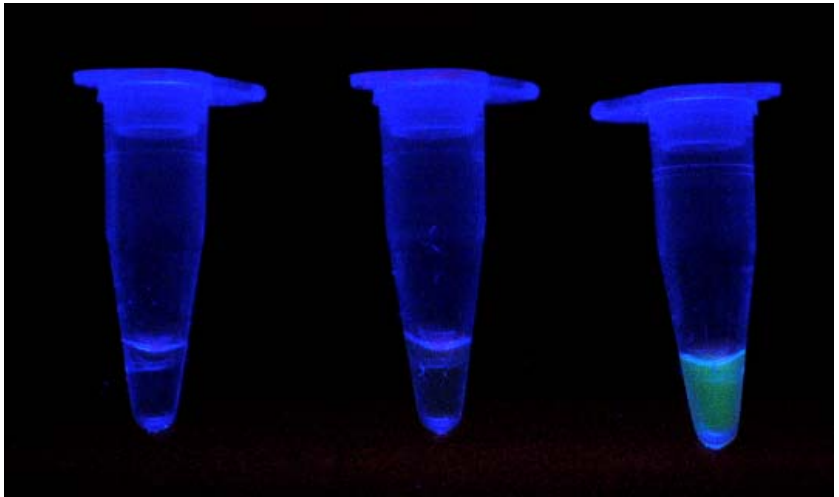
	Sensitivity
Conventional PCR	7.3%
Nested PCR	85.4%
RT-PCR	82.9%

Simple, rapid and sensitive detection of *Orientia tsutsugamushi* by loop-isothermal DNA amplification

TRSTMH 2008;102:1239

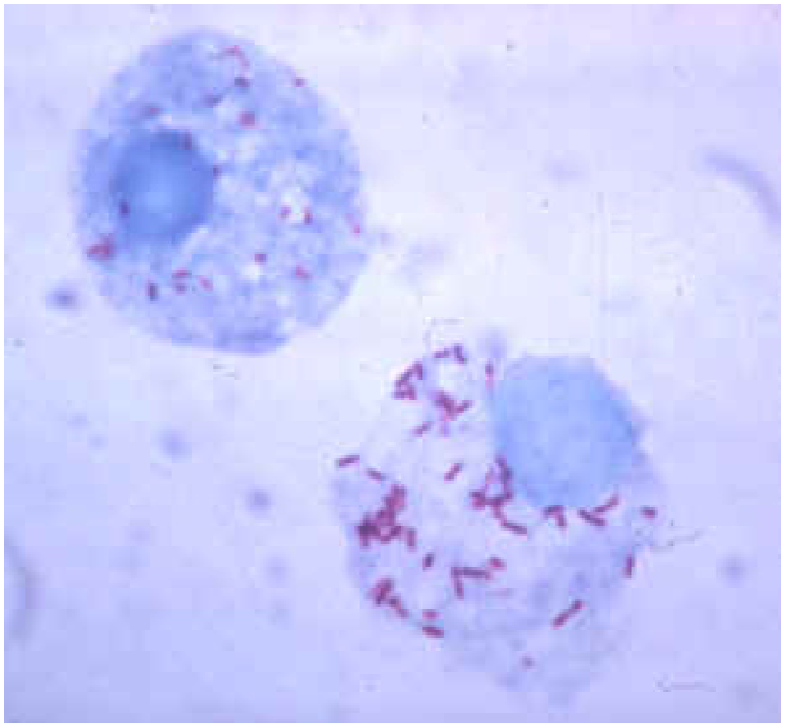
Daniel H. Paris[a,b,*], Stuart D. Blacksell[a,b], Paul N. Newton[b,c], Nicholas P.J. Day[a,b]





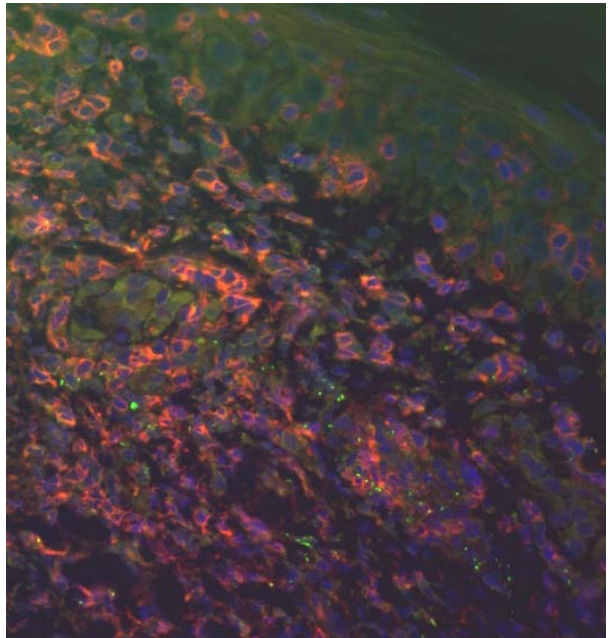
Rickettsioses in Asia - challenges

- Clinical epidemiology
- Diagnostics
- Treatment
  - Remains largely empirical
  - Good options but diagnosis needs to be thought of
  - Pregnancy
  - ?Resistance
- Pathobiology & pathophysiology
- Vaccines and prevention



Rickettsioses in Asia - challenges

- Clinical epidemiology
- Diagnostics
- Treatment
- Pathobiology & pathophysiology
  - Ecology, 1° host-pathogen interaction
  - Comparative genomics
  - Human immune response
  - Pathophysiology of disease
  - Informs diagnostics and vaccine development
- Vaccines and prevention



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PLoS NEGLECTED TROPICAL DISEASES

High Rates of Homologous Recombination in the Mite Endosymbiont and Opportunistic Human Pathogen *Orientia tsutsugamushi*

Piengchan Sonthayanon[1,2]*, Sharon J. Peacock[2,3], Wirongrong Chierakul[1,2], Vanaporn Wuthiekanun[2], Stuart D. Blacksell[2], Mathew T. G. Holden[4], Stephen D. Bentley[4], Edward J. Feil[5], Nicholas P. J. Day[2,6]

1 Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, **2** Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, **3** Department of Medicine, University of Cambridge, Cambridge, United Kingdom, **4** The Wellcome Trust Sanger Institute, Hinxton, United Kingdom, **5** Department of Biology and Biochemistry, University of Bath, Bath, United Kingdom, **6** Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom

PLoSNTD 2010;4:e752

Diversity of *Orientia tsutsugamushi* clinical isolates in Cambodia reveals active selection and recombination process

Veasna Duong [a,1], Kim Blassdell [a,1], Thinh Thi Xuan May [b], Lay Sreyrath [a], Laurent Gavotte [c], Serge Morand [c], Roger Frutos [d,*], Philippe Buchy [a,**]

[a] *Virology Unit, Institut Pasteur in Cambodia, 5 Monivong blvd, PO Box 983, Phnom Penh, Cambodia*
[b] *Virology Department, Institut Pasteur in Nha Trang, 10 Tran Phu Street, Nha Trang, Viet Nam*
[c] *UM2, ISEM, UMR 5554, CNRS-UM2-IRD, Université Montpellier 2 CC065, Place E. Bataillon, 34095 Montpellier Cedex 5, France*
[d] *Cirad, UMR 17, Cirad-Ird, TA-A17/G, Campus International de Baillarguet, 34398 Montpellier Cedex 5, France*

Infection, genetics and evolution 2010

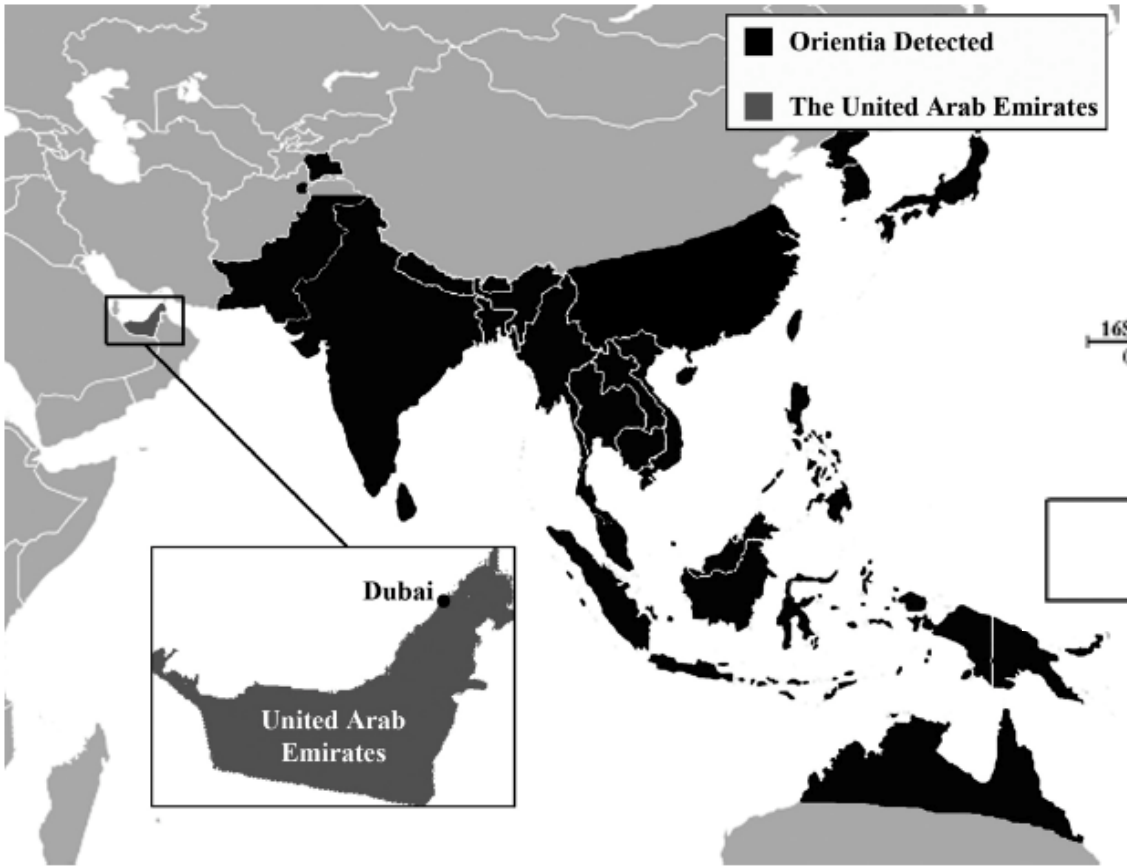
- Very high recombination rates despite vertical transovarial transmission
- Multiple genotype infections in man
- Does recombination occur in mites or rodents (or both)?

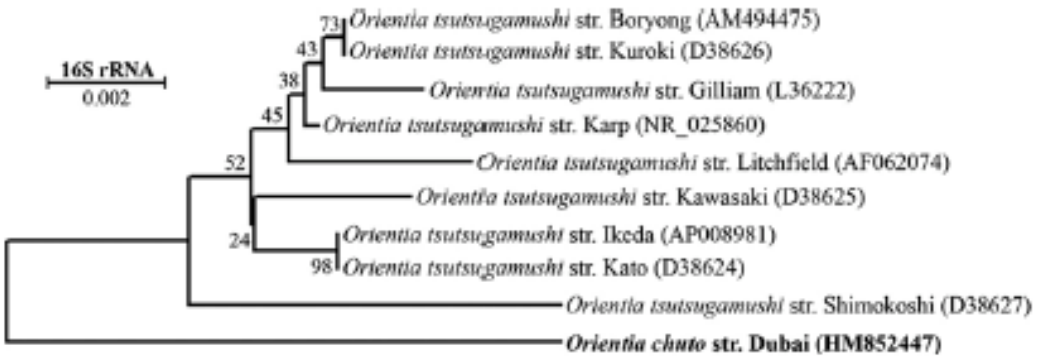
JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2010, p. 4404–4409 Vol. 48, No. 12
0095-1137/10/$12.00 doi:10.1128/JCM.01526-10

Isolation of a Novel *Orientia* Species (*O. chuto* sp. nov.) from a Patient Infected in Dubai[▽]

Leonard Izzard,[1,2] Andrew Fuller,[3] Stuart D. Blacksell,[4,5] Daniel H. Paris,[4,5] Allen L. Richards,[4,6,7] Nuntipa Aukkanit,[4,5] Chelsea Nguyen,[1] Ju Jiang,[6] Stan Fenwick,[2] Nicholas P. J. Day,[4] Stephen Graves,[1] and John Stenos[1,2]*

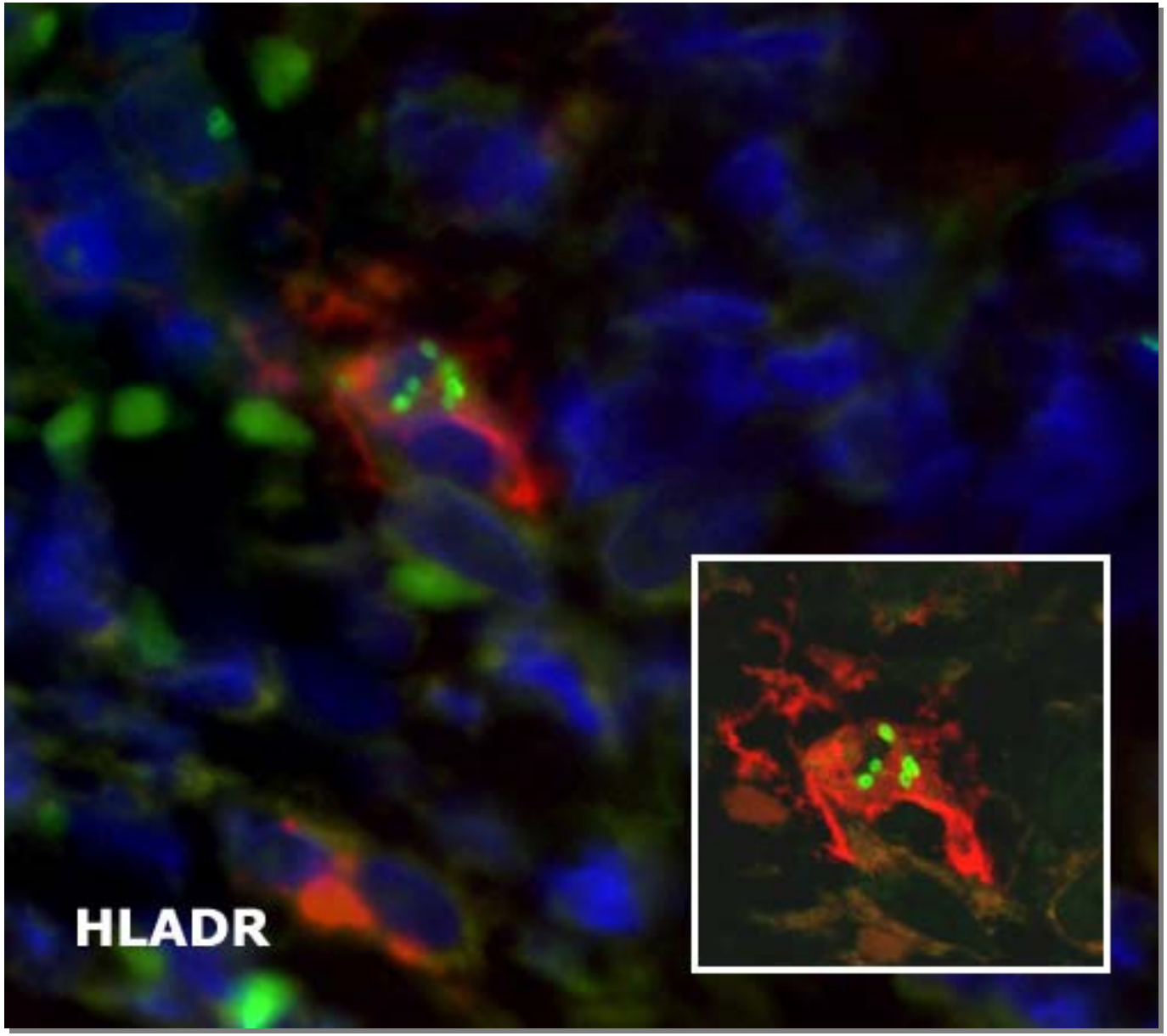
Eschar
Fever
Myalgia
Rash
Lymphadenopathy
Raised transaminases





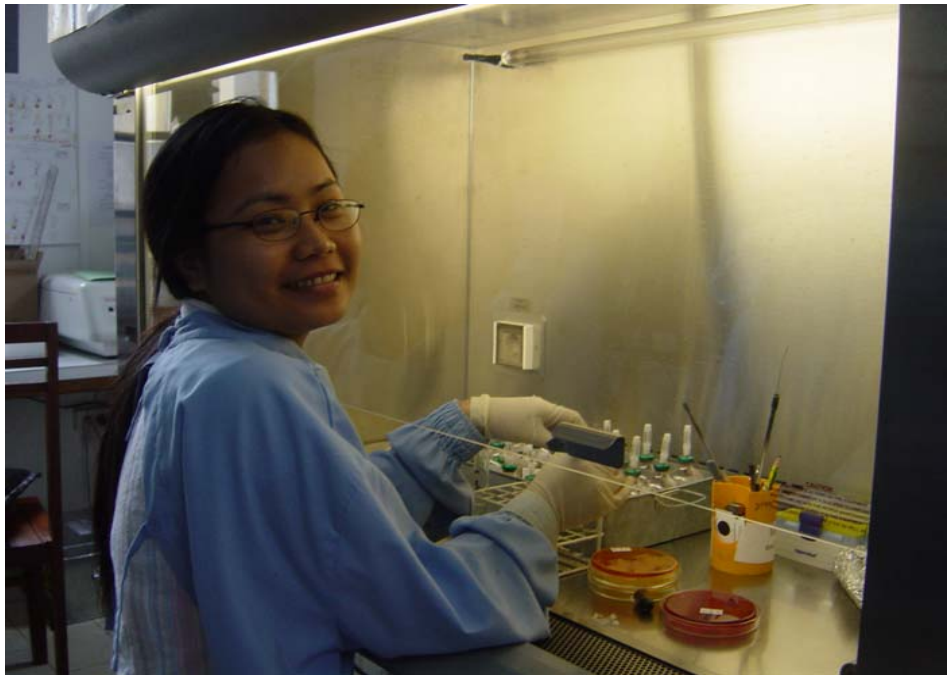
Positive ST serology
Treated successfully with doxycycline

O. tsutsugamushi in a human eschar



Rickettsioses in Asia - challenges

- Clinical epidemiology
- Diagnostics
- Treatment
- Pathobiology & pathophysiology
- Vaccines and prevention
  - Immunopathology poorly understood
  - Highly antigenically variable
  - Ecology



Acknowledgements

- Rattanaphone Phetsouvanh
- Piengchan Sonthayanon
- Wirongrong Chierakul
- Yupin Suputtamongkol
- Manivanh Vongsouvath
- Stuart Blacksell
- Daniel Paris
- Gareth Turner
- Paul Newton
- Staff of Mahosot Hospital, SMRU and FTM, Bangkok
- The Wellcome Trust