

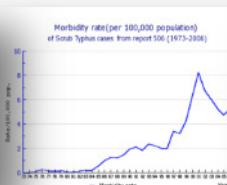
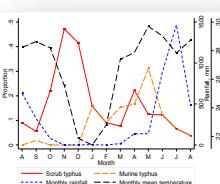
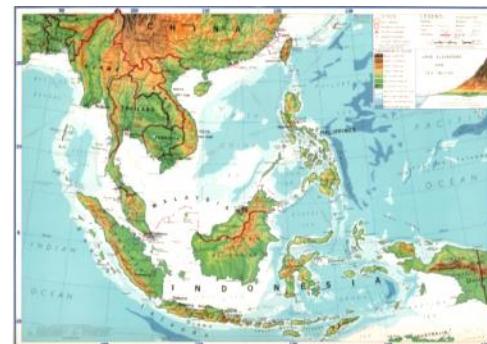
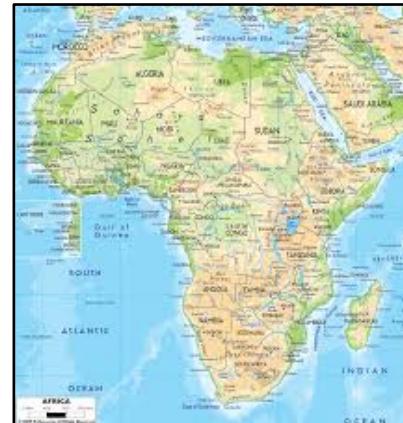
Daniel H. Paris, MD, PhD, DTM&H

Medical Director

Head, Dept. of Medicine

Swiss Tropical and Public Health Institute

Rickettsia and the Non-Malaria Fever Complex



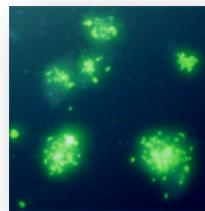
“Fever” – “Febrile illnesses” - “Undifferentiated Fever”

Malaria

Declining numbers / Artemisinin resistance

“last man standing vs. emerging threat”

“rule out malaria first”



Typhus-like illnesses

Dengue / Chikungunya

Scrub typhus / Murine typhus

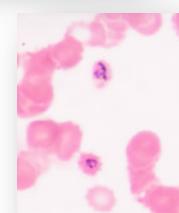
Leptospirosis

JEV / Zika

Melioidosis

Typhoid (India / Pakistan / Bangladesh)

Q fever, Brucellosis



Fever – the major complaint ...

*Fever is the most common presentation to medical attention
in tropical countries*



*... but the cause of most febrile illness episodes
remains unknown ...*

The importance of clinical epidemiology...

To inform control programs

To inform empirical treatment guidelines

To inform on diagnostic and treatment algorithms

To inform which diagnostic tests are clinically useful

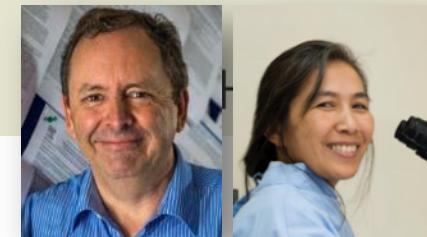
To help identify emerging infectious diseases

1. To define the disease 'background'
2. Diagnostic capacity in place ready to detect EIDs



“Knowing what’s out there ...”

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%

Is this generalisable to the whole of Laos? Of SE Asia? Elsewhere?

Causes of non-malaria fever in Laos

2008 - 2010

Rural Laos: n=1,938 febrile patients admitted, n=799 (41%) w/ diagnosis

Difficulties – serology, endemic background titers (?)

Only culture, antigen, and nucleic acid detection assays (conservative)

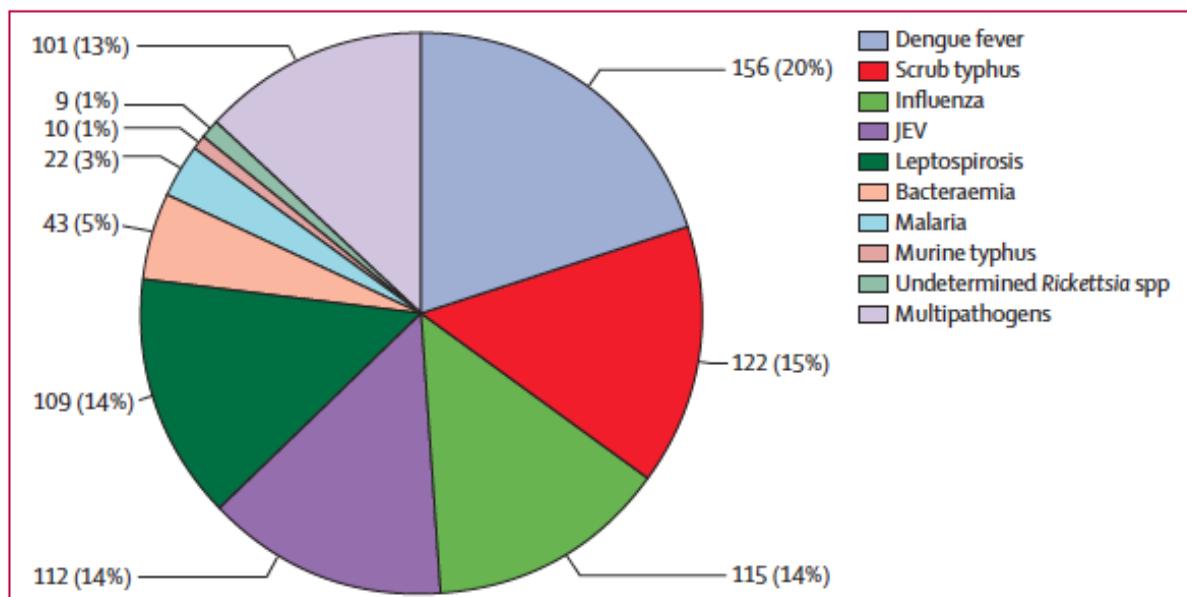
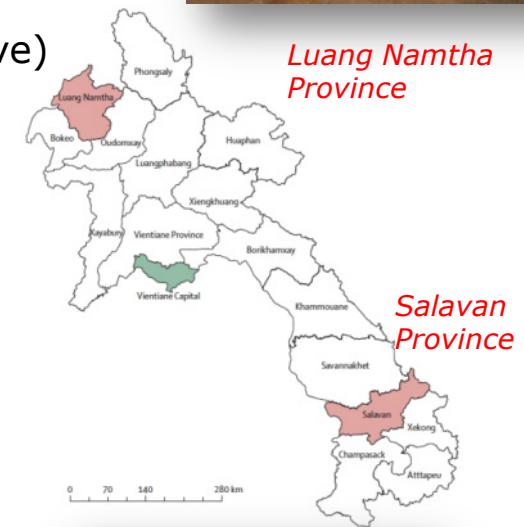
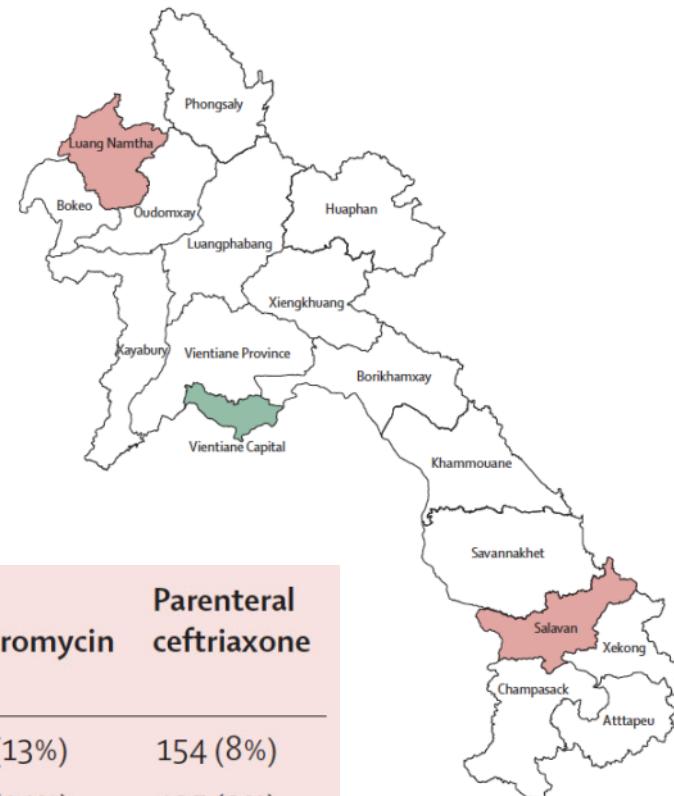


Figure 2: Diagnoses for patients (N=799) at both study sites, with use of only culture, antigen, and nucleic acid detection assays (conservative definition)



Empirical treatment...

- JEV, typhoid & leptospirosis more common in Luang Namtha
- Malaria & dengue more common in Salavan



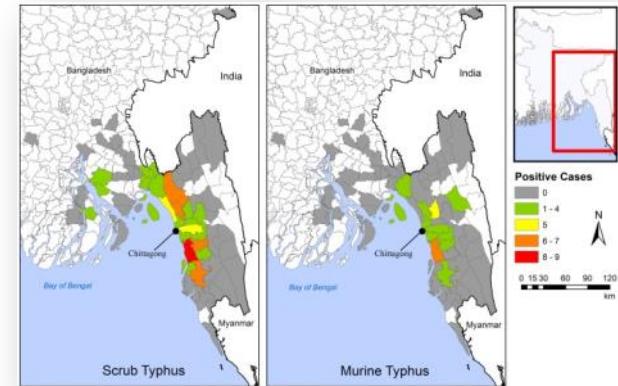
	Number with potentially antibiotic-susceptible pathogens	Oral doxycycline	Oral ofloxacin	Oral azithromycin	Parenteral ceftriaxone
All (N=1938)	293 (15%)	240 (12%)	41 (2%)	258 (13%)	154 (8%)
Luang Namtha (n=1390)	223 (16%)	184 (13%)	29 (2%)	198 (14%)	125 (9%)
Salavan (n=548)	70 (13%)	56 (10%)	12 (2%)	60 (11%)	29 (5%)

82% !!!

Doxycycline may be a cost-effective empirical treatment in those with negative malaria and dengue rapid tests!

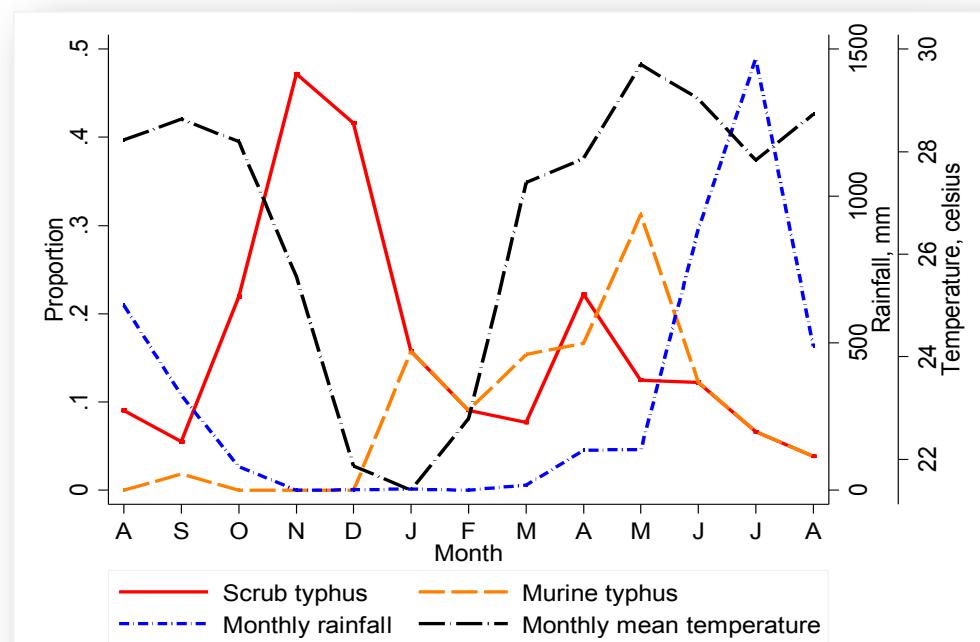
Bangladesh Fever study

Hospitalised, fever <14 days
n=416 over one full calendar year



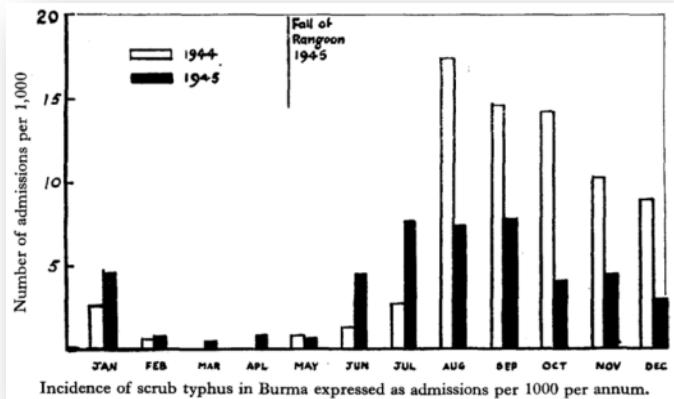
Rickettsial illness	23 %
Scrub typhus	16%
<i>Rickettsia</i> spp.	7%
- Murine typhus, SFG, <i>R. felis</i>	

Use of stringent diagnostic criteria:
Dg: PCR / sequencing
paired dynamic serology

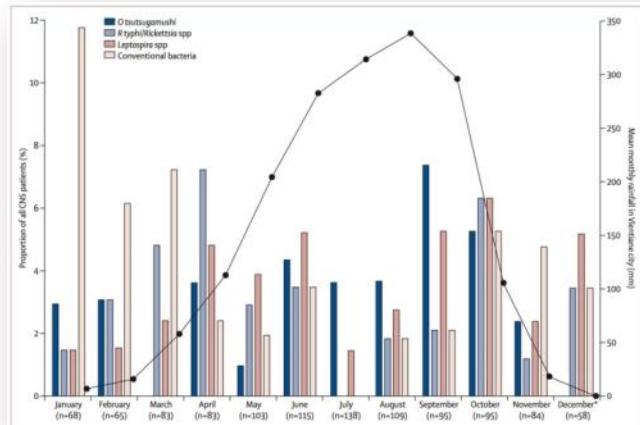


Fever Studies – *some thoughts*

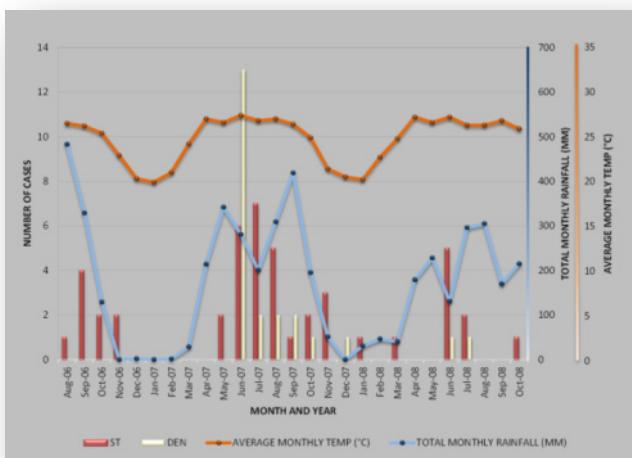
Myanmar



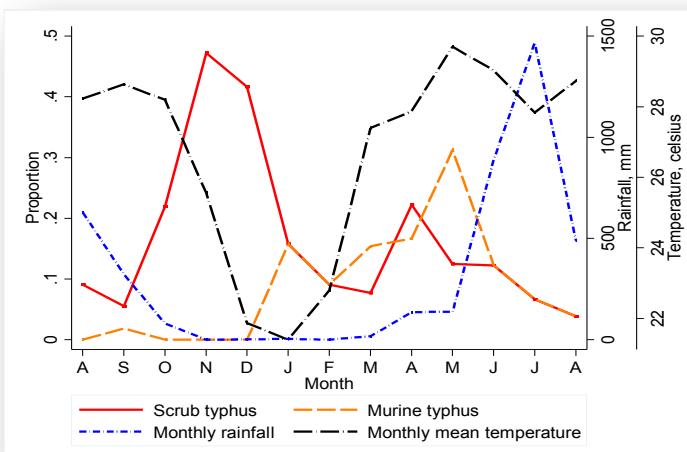
Laos



N-Thailand



Bangladesh



Typhus in SEA

Thailand

"Dengue-like illness"

Malaysia

"Typhus-like illness"

Laos

ST and MT (and SFG)

Vietnam

combined = leading cause of treatable undifferentiated febrile illnesses

Cambodia

Myanmar

- burden 15% ST, 10% MT

Bangladesh

- urban / rural distribution

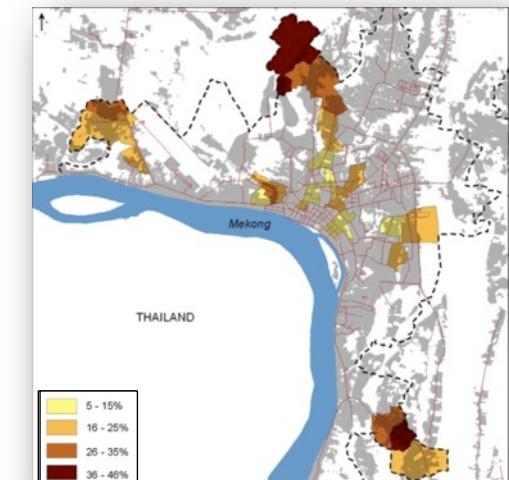
India

- incidence 3% pop/mon

... ?! etc.

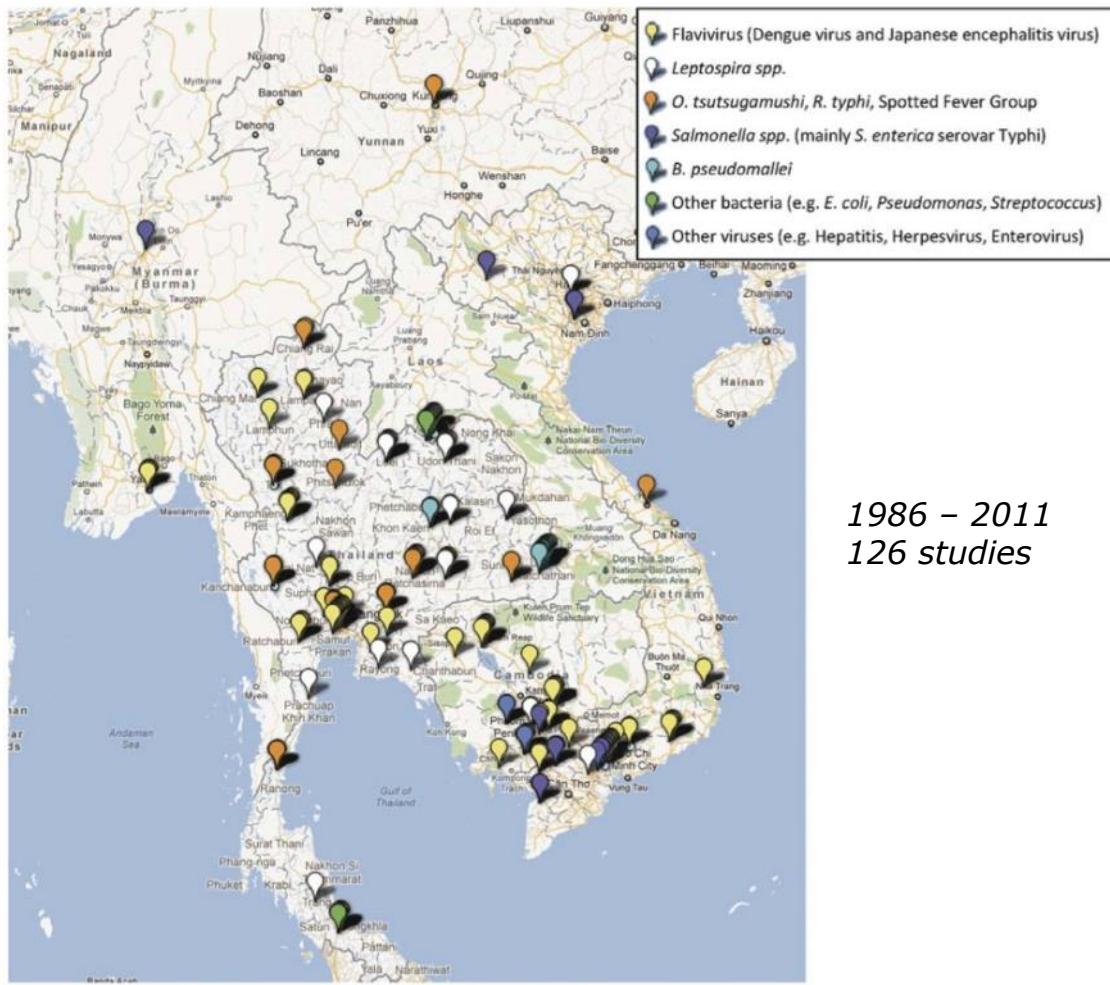
- seroprevalence 30-50%

- reversion to seronegativity approx. 40-50% per year



**Seriously underreported and underestimated ...
Clinical and diagnostic limitations**

Mapping Non-Malaria Febrile Illnesses



Most frequent reported diseases/pathogens:

- *Dengue*
- *Rickettsial infections*
- *Leptospirosis*
- *Typhoid*
- *Melioidosis*
- *JEV*

Mapping the Aetiology of Non-Malarial Febrile Illness in Southeast Asia 2012

"Typhus-like Illnesses"

Dengue

Rickettsioses

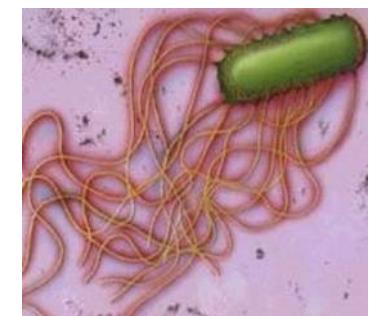
1. scrub typhus (*Orientia tsutsugamushi*)
2. murine typhus (*Rickettsia typhi*)
3. spotted fever rickettsiosis (SFG)

Leptospirosis

Typhoid

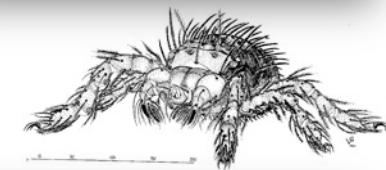
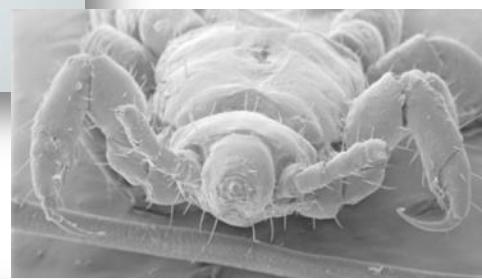
Uncomplicated Malaria

Bacterial meningitis



! first rule out malaria - then consider typhus !

“What are Rickettsioses ?!”



Rickettsia spp. / *Orientia* spp.

Obligate intracellular bacteria (1um-2um)

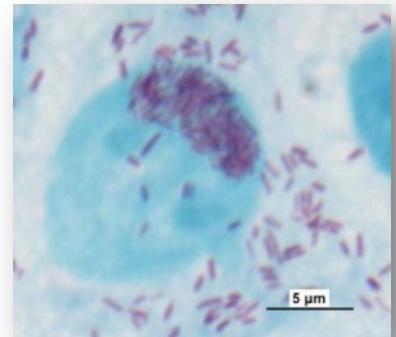
Gram-negative (*Orientia* – Giemsa/Gimenez)

Culture in cells (yolk sac / tissue culture)

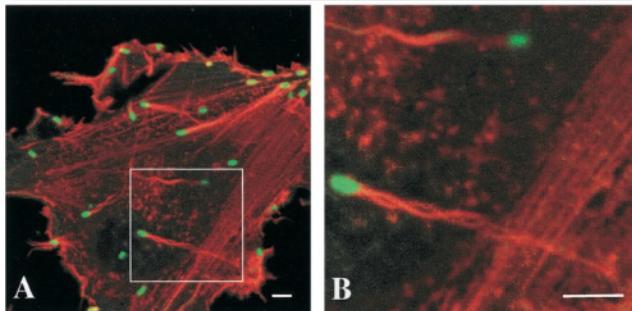
Orientia lack peptidoglycan and LPS

“Budding” from host cell – virus-like

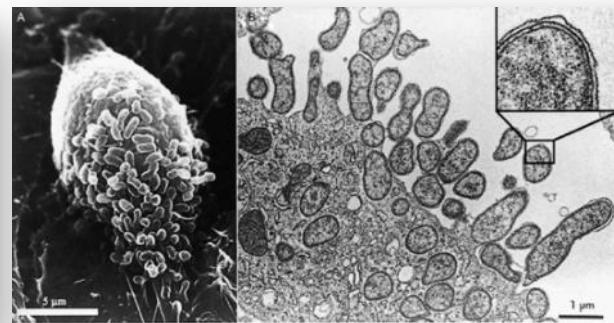
Genome (OT largest – RT smallest)



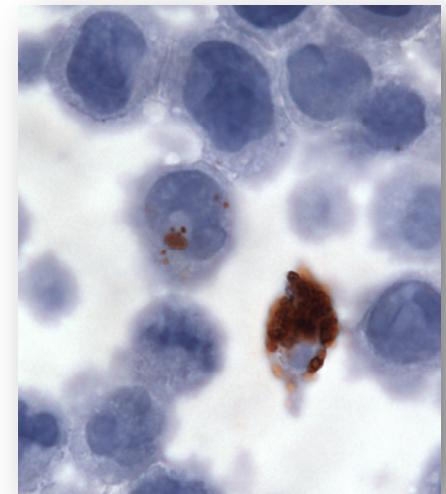
R. bellii - Gimenez



SFG Rickettsia – actin tails



O. tsutsugamushi - budding

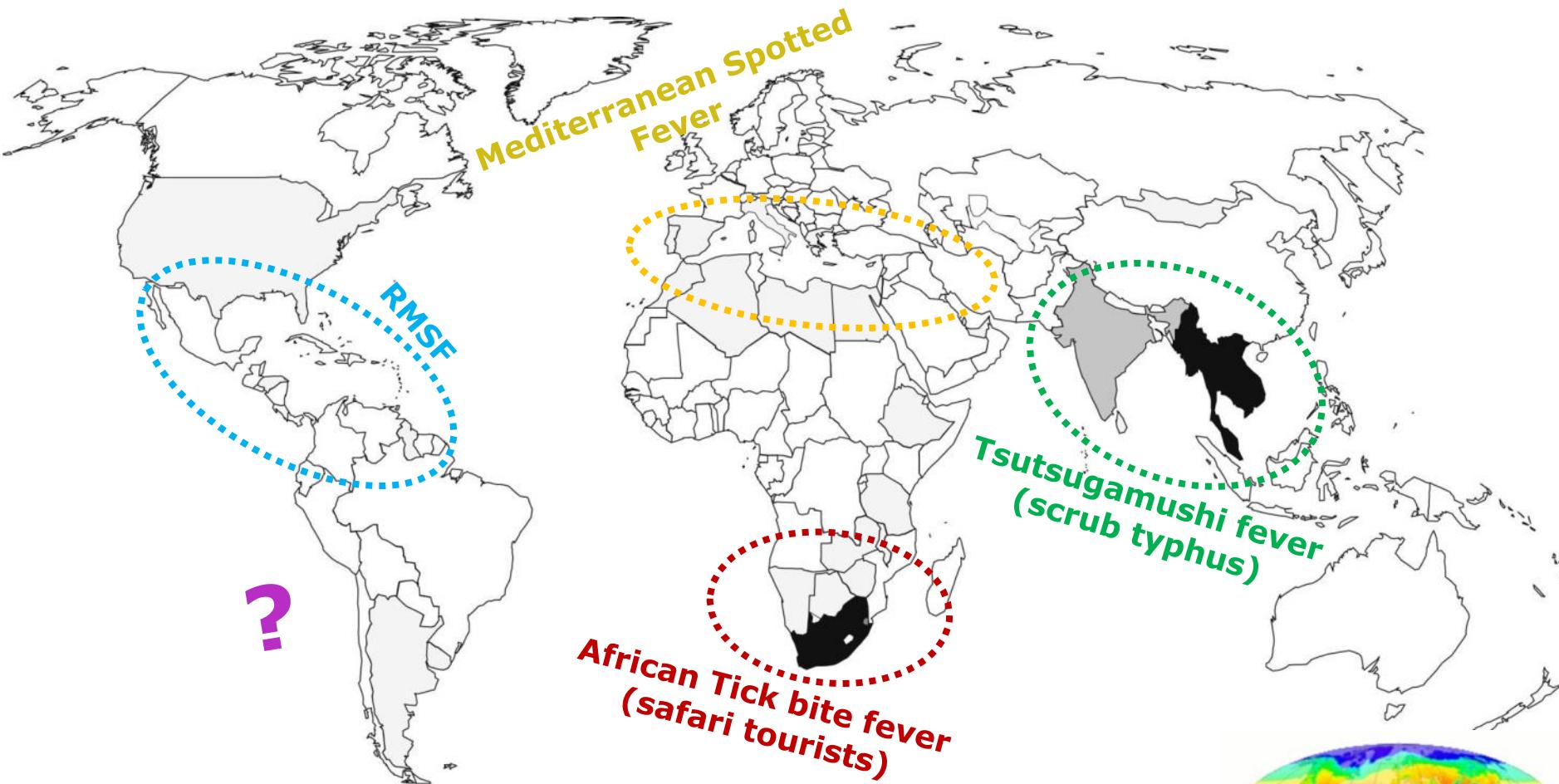


O. tsutsugamushi – mono/mcp

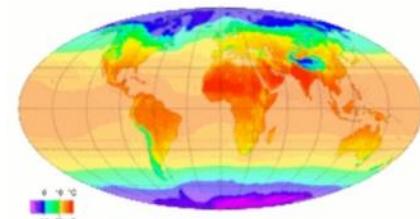
Rickettsial Diseases

- **Typhus Group**
 - Epidemic louse-borne typhus *R. prowazekii* lice
 - Endemic flea-borne / **Murine typhus** *R. typhi* rat fleas
- **Scrub typhus Group**
 - **Scrub typhus** / Tsutsugamushi fever *O. tsutsugamushi* mites
- **Spotted Fever Group**
 - Worldwide distribution,
esp. Europe/Africa/America **Tick-borne Rickettsioses** ticks
- **Transitional Rickettsia ("emerging forms")**
 - R. felis* / *R. felis*-like / *R. australis* / *R. akari* fleas, ticks, mites
- Coxiella / Q-fever inhalation, ingestion
- Ehrlichia ticks
- Anaplasma ticks
- Neorickettsia (*sennetsu fever* [mononucleosis-like symptoms]) fish

Rickettsioses in travellers



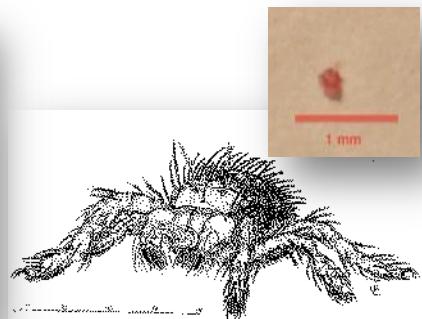
- One to five cases of rickettsioses reported in travelers during the last ten years
- Six to ten cases of rickettsioses reported in travelers during the last ten years
- Eleven to twenty cases of rickettsioses reported in travelers during the last ten years (in Swaziland)
- More than twenty cases of rickettsioses reported in the last 10 years



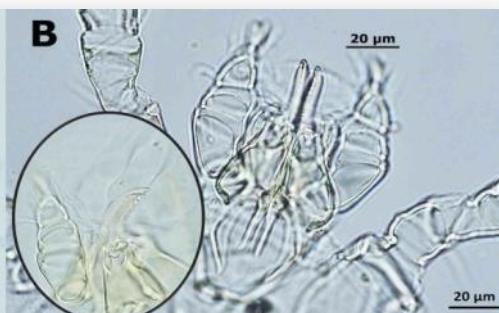
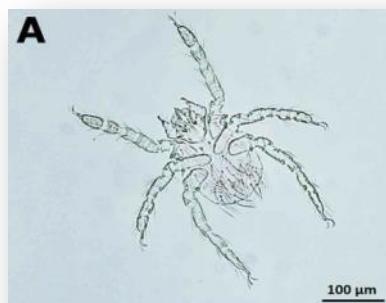
Scrub typhus

Orientia tsutsugamushi

Mites



***Leptotrombidium* mites**



Murine Typhus

Rickettsia typhi

Fleas



***Xsenopsylla cheopis* (rat flea)**



Cat flea
Ctenocephalides felis

Pronotal comb

Eye

Genal comb

Clinical Presentation

Eschar

Rash “spotted fever” – “spotless” spotted fever(!)
 “exanthematic typhus”

“Typhus” - *typhos* [smoky, hazy]
 neurological symptoms

Complications

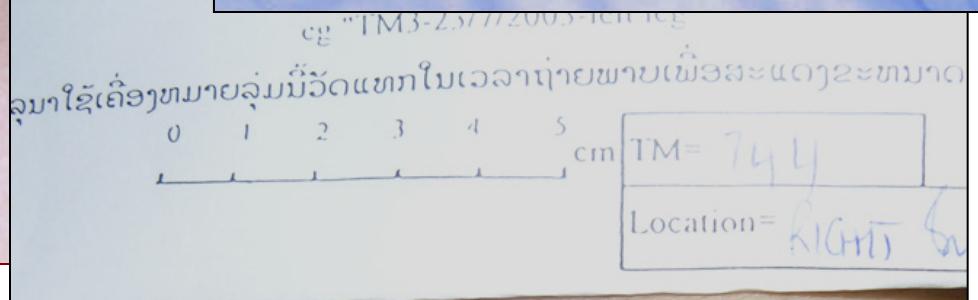
1. Meningo-encephalitis
2. Pneumonitis – ARDS
3. Acute renal failure
4. Severe hepatitis
5. Myocarditis
6. Coagulopathies – DIC



Typhus: Coma - delir - confusion

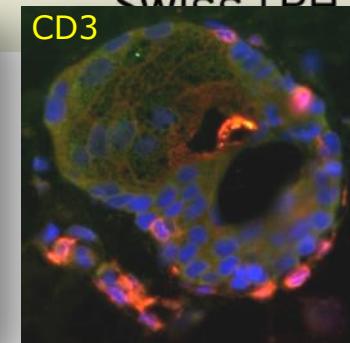
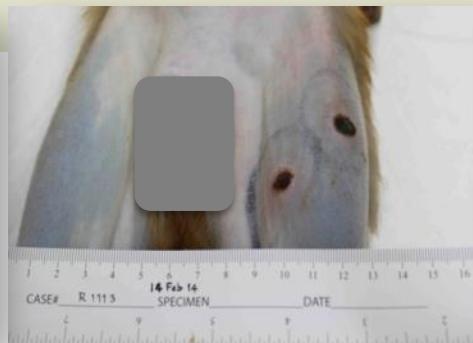


Eschars



Skin Rash

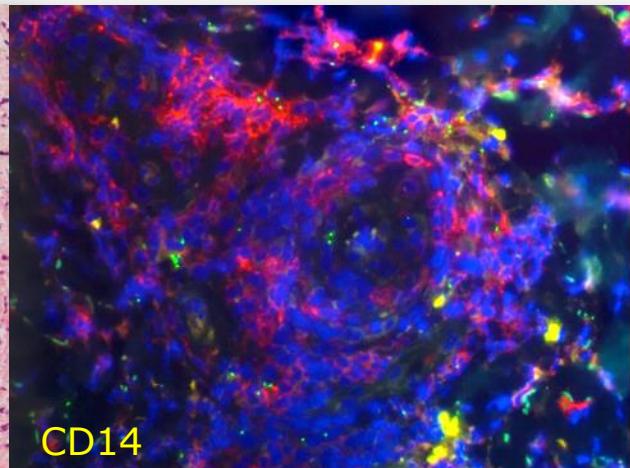
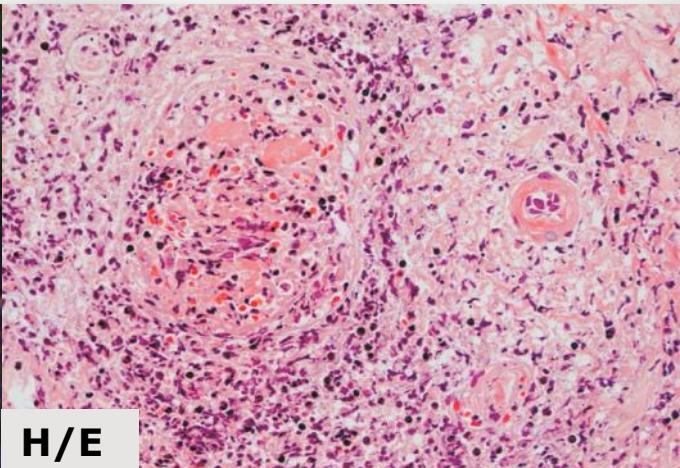
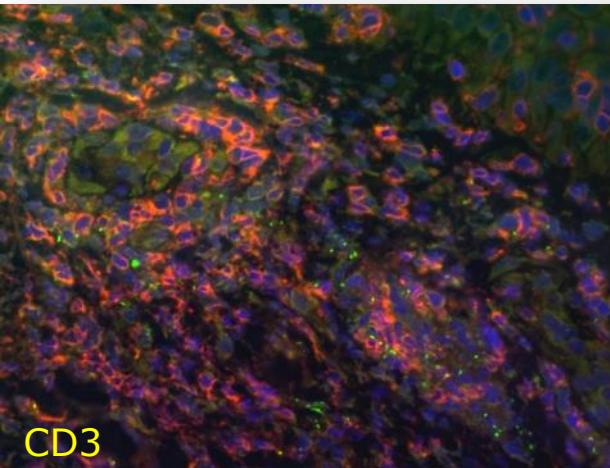




Pathogenic mechanisms (Orientia vs. Rickettsia)

Systemic "vasculitis" - vasculopathy

?!! *endothelial infection vs. mononuclear perivascular infiltrates*



Typhus and Pregnancy



... how does vasculopathy affect pregnancy / placenta?!

highly under appreciated!

Less than 100 women with a known pregnancy outcome in 18 years!!!

Total n= 97 cases (FUP \geq 28 weeks gestation)



17% Stillbirths

42% Poor neonatal outcomes [*stillborn / premature / SGA*]

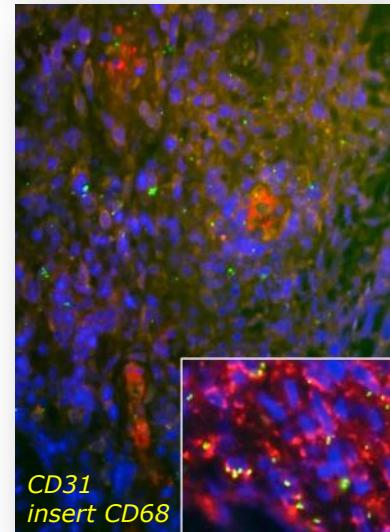
no linear trend per trimester (!)

Prospective longitudinal comparison to malaria

(same study site / period / SMRU)

Typhus - preterm 14% - LBW (10) 22%

Malaria - preterm 7% - LBW (10) 17%



Differential Diagnosis

"Typhus-like illness"

- Leptospirosis
- Murine Typhus
- Spotted Fever Rickettsiosis
- Dengue
- Japanese Encephalitis
- Typhoid (*Salm. Typhi*)
- Bacterial meningitis
- (Malaria)



Treatment

Caveat: Betalactams and Fluoroquinolones do not work!

Current regimens

Doxycycline 2x100mg p.os. /d for 7-10 days

Azithromycin 500mg p.os./d for 7-10 days

Chloramphenicol (seldomly used, but excellent)

Rifampicin (not used due to interactions with Doxy and Azithro – hepatic cyt P450 induction reduces plasma levels)

Delayed treatment response :

If prolonged fever clearance consider Doxy+Azithro combination

Pediatric dosage:

45kg or less - 2.2 mg/kg p.os./d (given once per day or in 2 divided doses)

45-60 kg - 100 mg p.os./d (given once per day or in 2 divided doses)

>60kg and adults 100mg p.os./d (given 2x daily)

Empirical coverage of typhus, leptospirosis and typhoid:

Azithromycin 1gr/d for 7 days (UK)



Typhus: Coma – delir - confusion

Untreated mortality

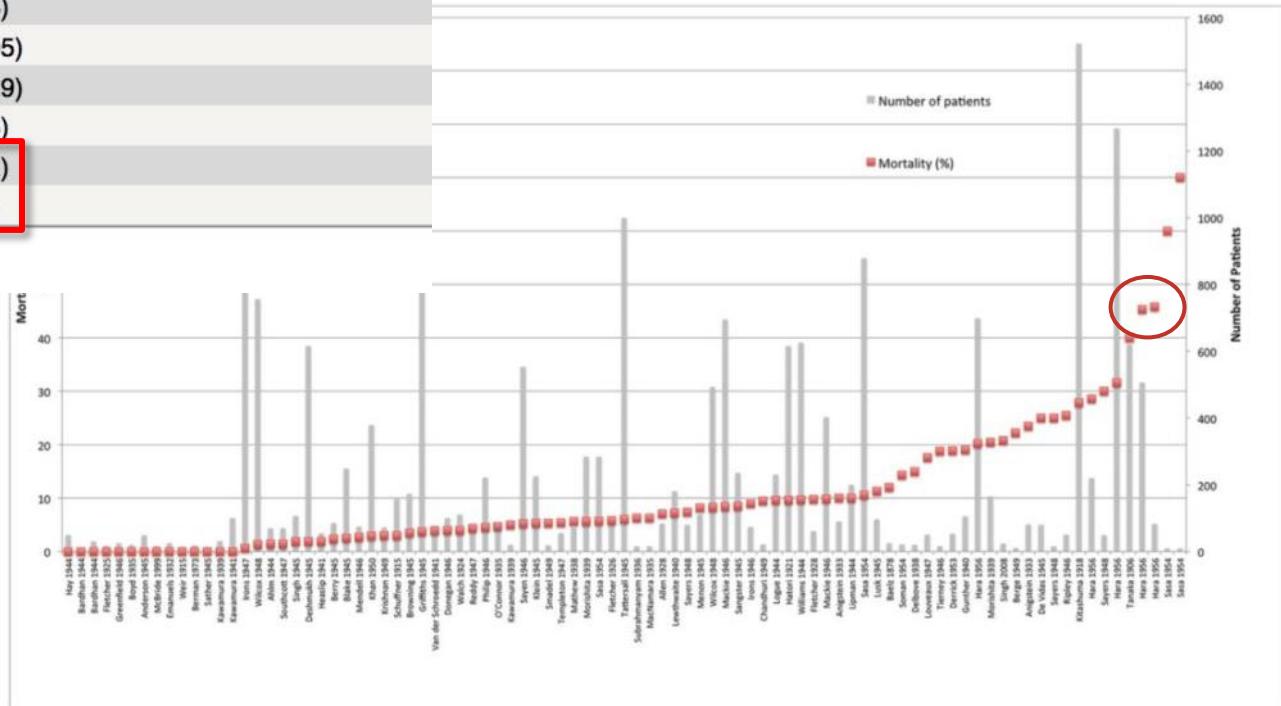
Approx. 6 - 9%

Table 2. Patient mortality by age.

Age	Number of Patient Series	Overall % Mortality (Number of deaths / Total number of patients across series)
1–10	6	11.1 (20/180)
11–20	12	11.0 (72/653)
21–30	12	12.0 (109/905)
31–40	10	13.9 (101/729)
41–50	11	18.7 (74/396)
51–60	7	45.6 (92/242)
61+	4	59.8 (52/87)

doi:10.1371/journal.pntd.0003971.t002

strains / age / vectors (?)
bacterial virulence (?)



No data for DALYs, and YLLs and YLDs available!



Doxycycline

Doxycycline is not dangerous and its classification misleading;

- *Teratogenicity during pregnancy*
- *Permanent tooth-staining (pregnancy / children <8 years)*
- *Hepatotoxicity*
- *Permanent inhibitory bone growth effects*

Doxycycline is safe in early pregnancy ($\leq 25w$) possibly throughout pregnancy and safe for children at the current dosage regimes !!!

- *if daily dosage is 200mg/day for 14 days*

→ Poor neonatal outcome vs. consequences of doxycycline side effects

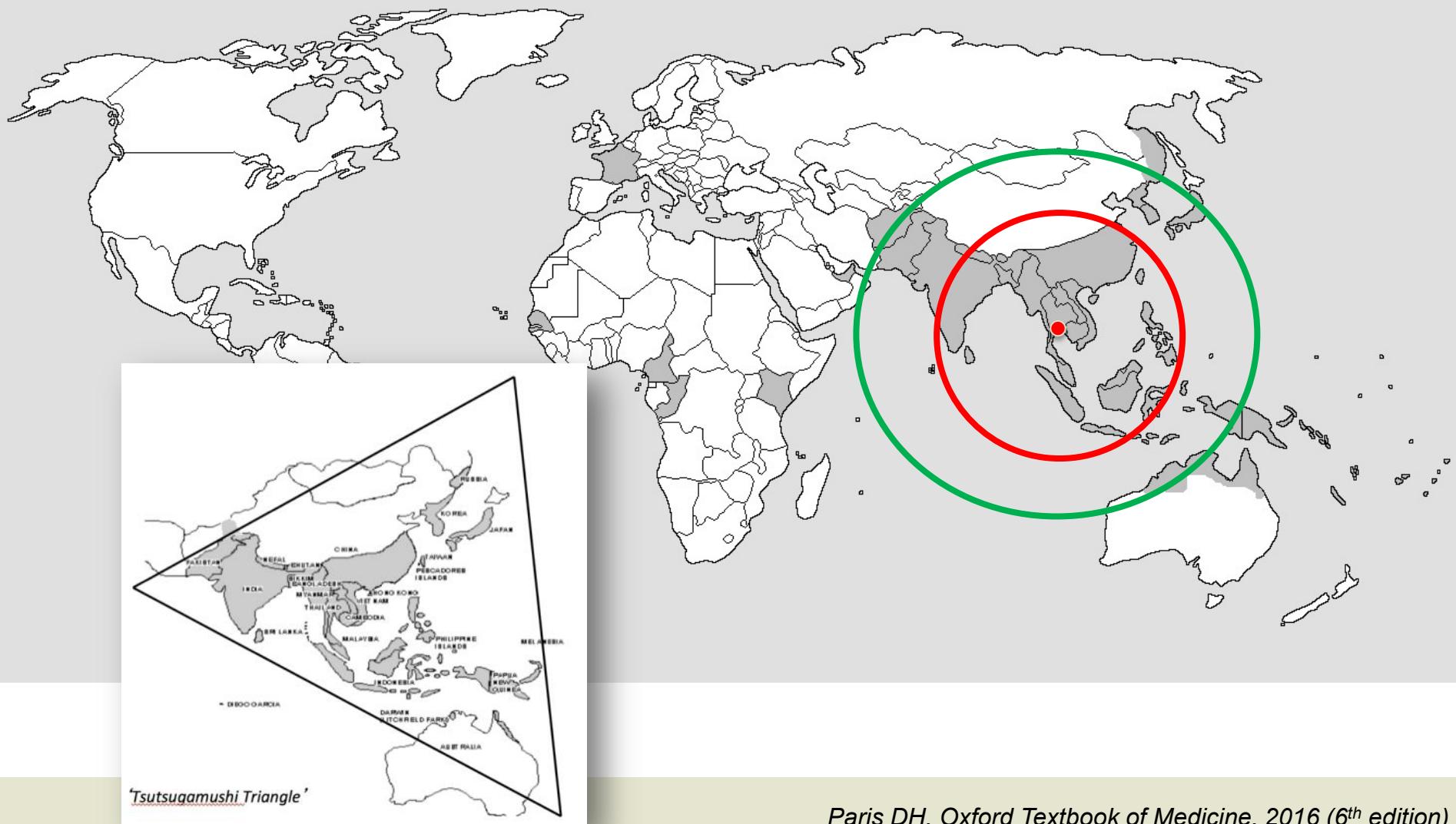
Change of US FDA pregnancy classification to evidence-based approach

- *Clinical treatment trials*
- *Adequate evaluation of doxycycline*
- *Dosage-optimization pharmacokinetic studies*
- *Empirical treatment of undifferentiated febrile illnesses, esp. pregnancy and children*

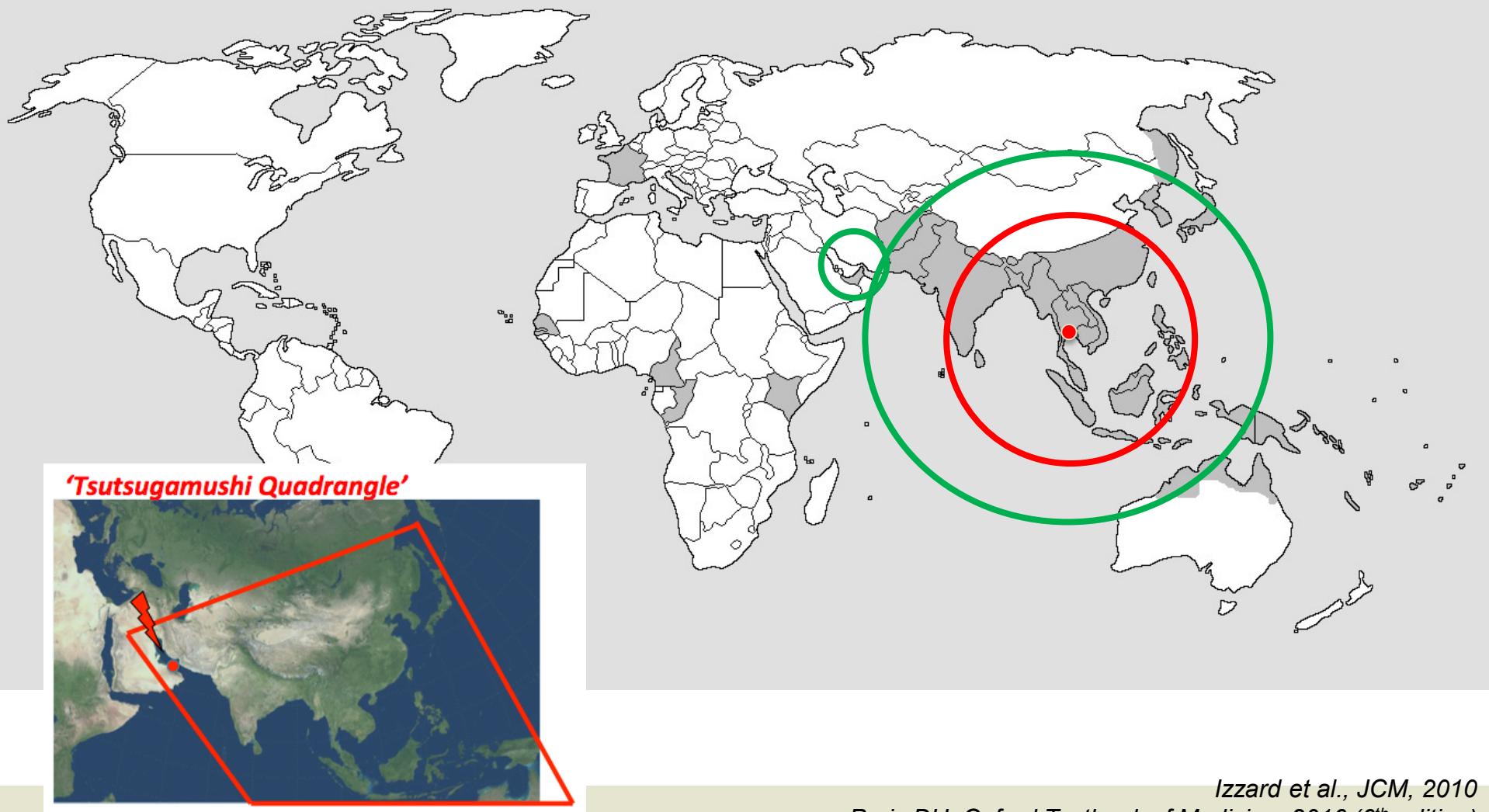
Bangkok ... half of the world's population within a 2'000 mile radius ... !



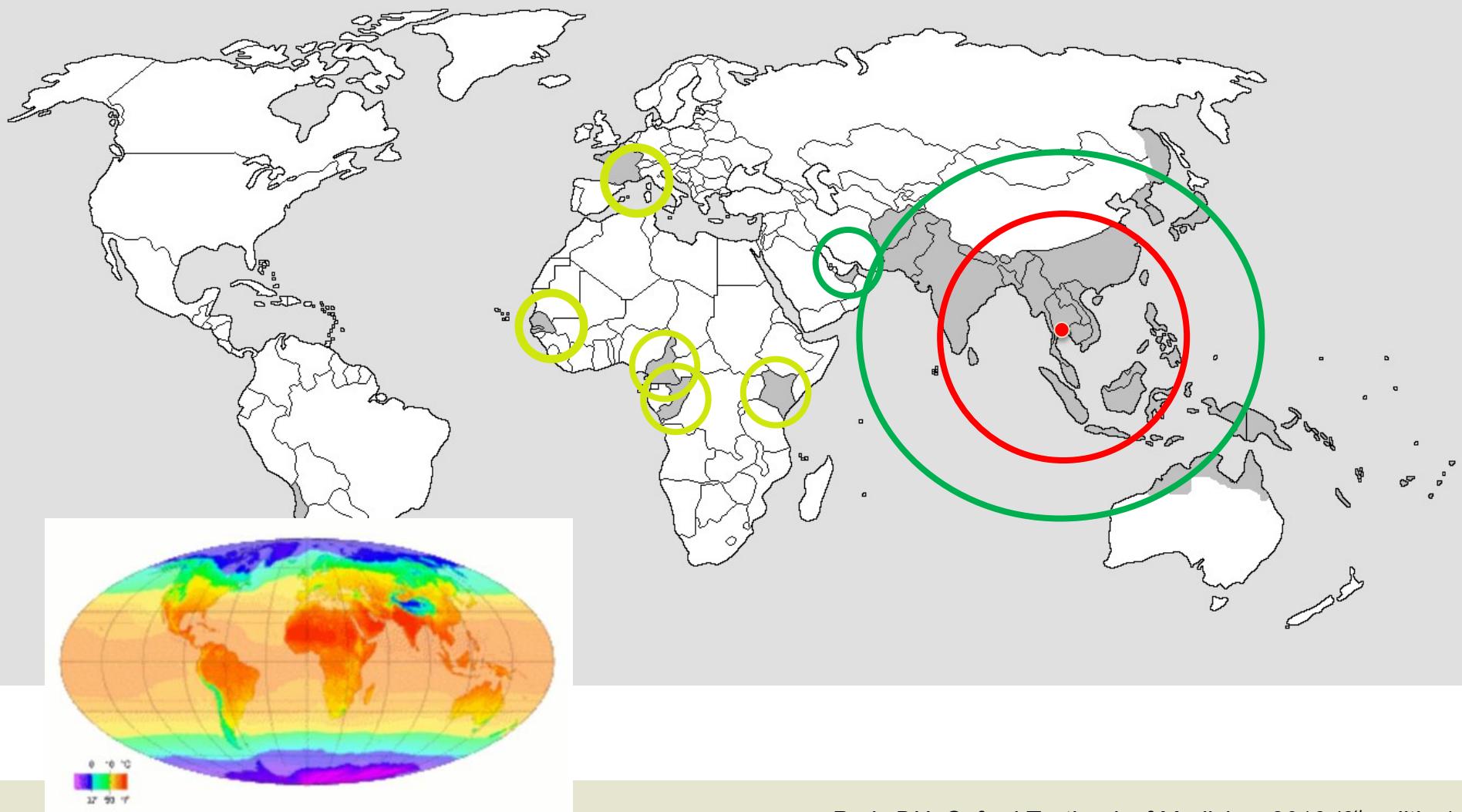
... >95% of reports of scrub typhus ...



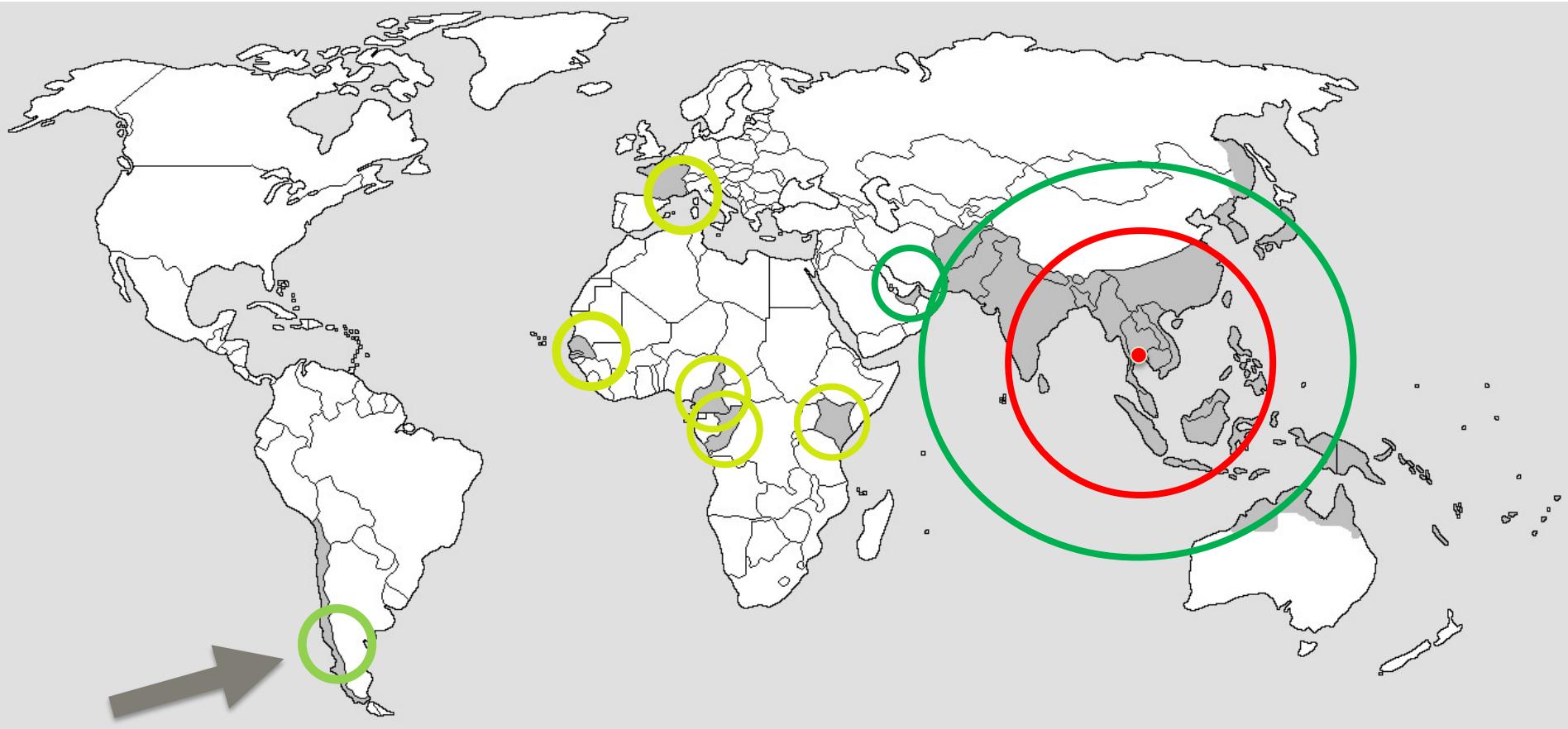
... potential global tropical / subtropical distribution ... ?!



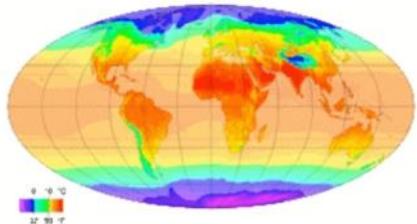
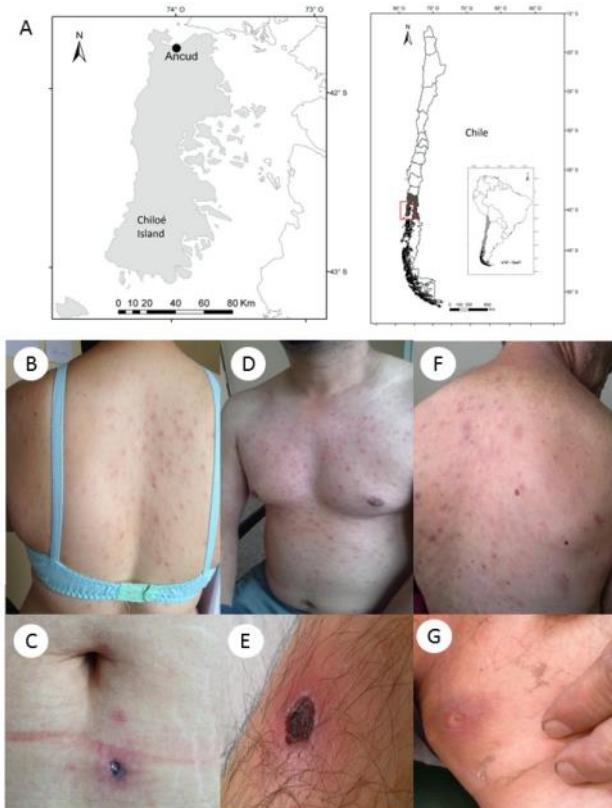
... potential global tropical / subtropical distribution ... ?!



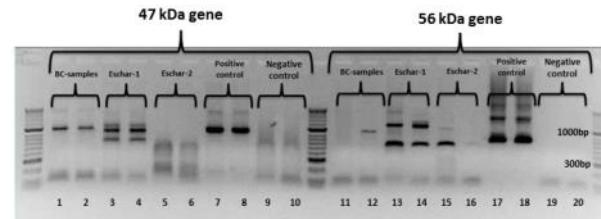
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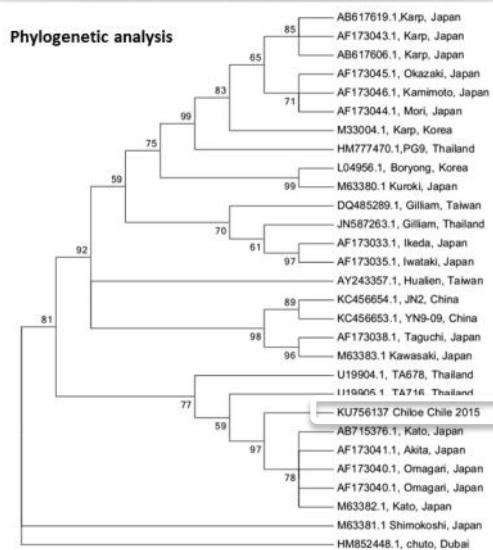
Scrub typhus in Chile – a paradigm shift



A Agarose gel electrophoresis of PCR products



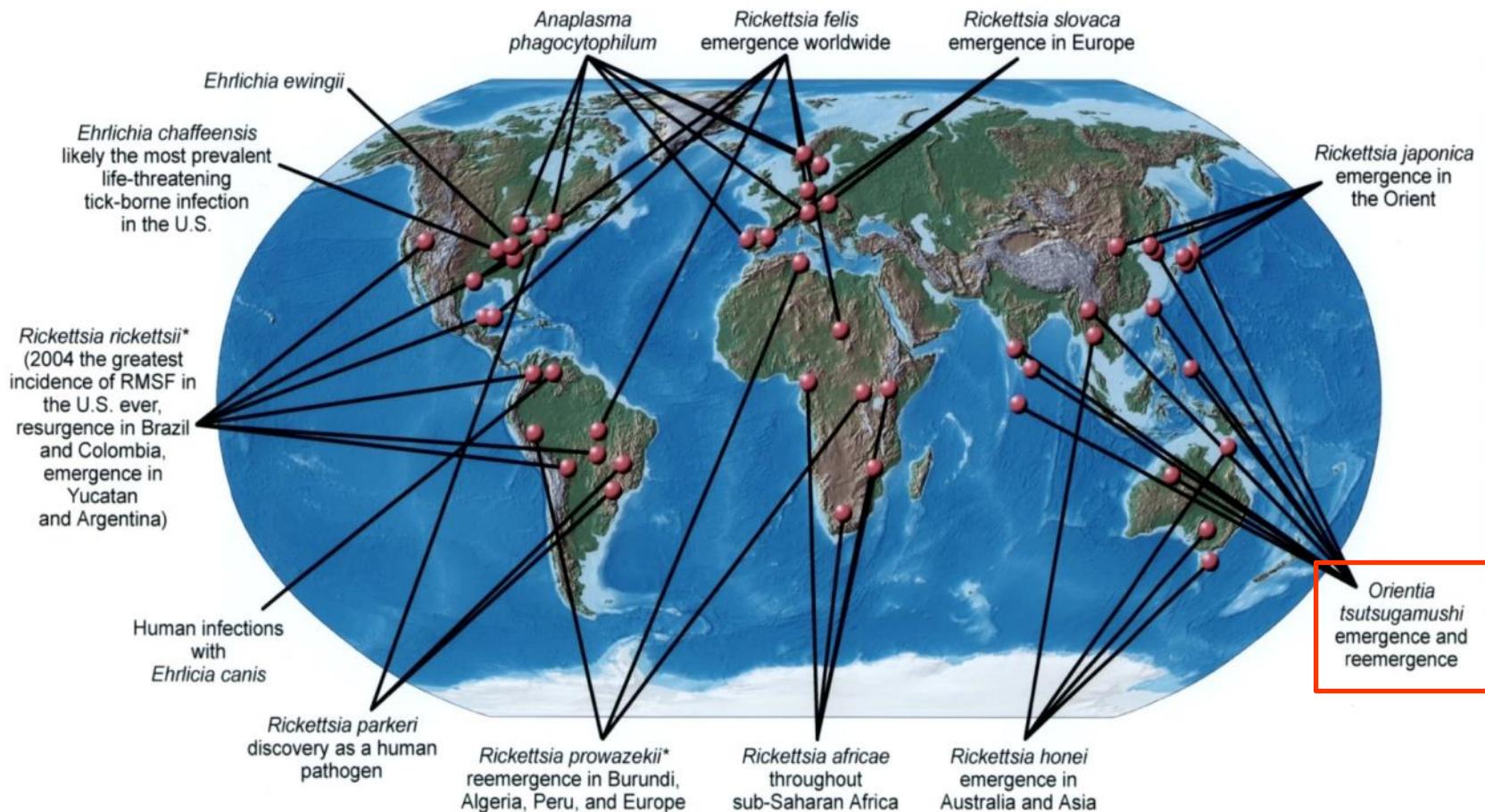
B Phylogenetic analysis



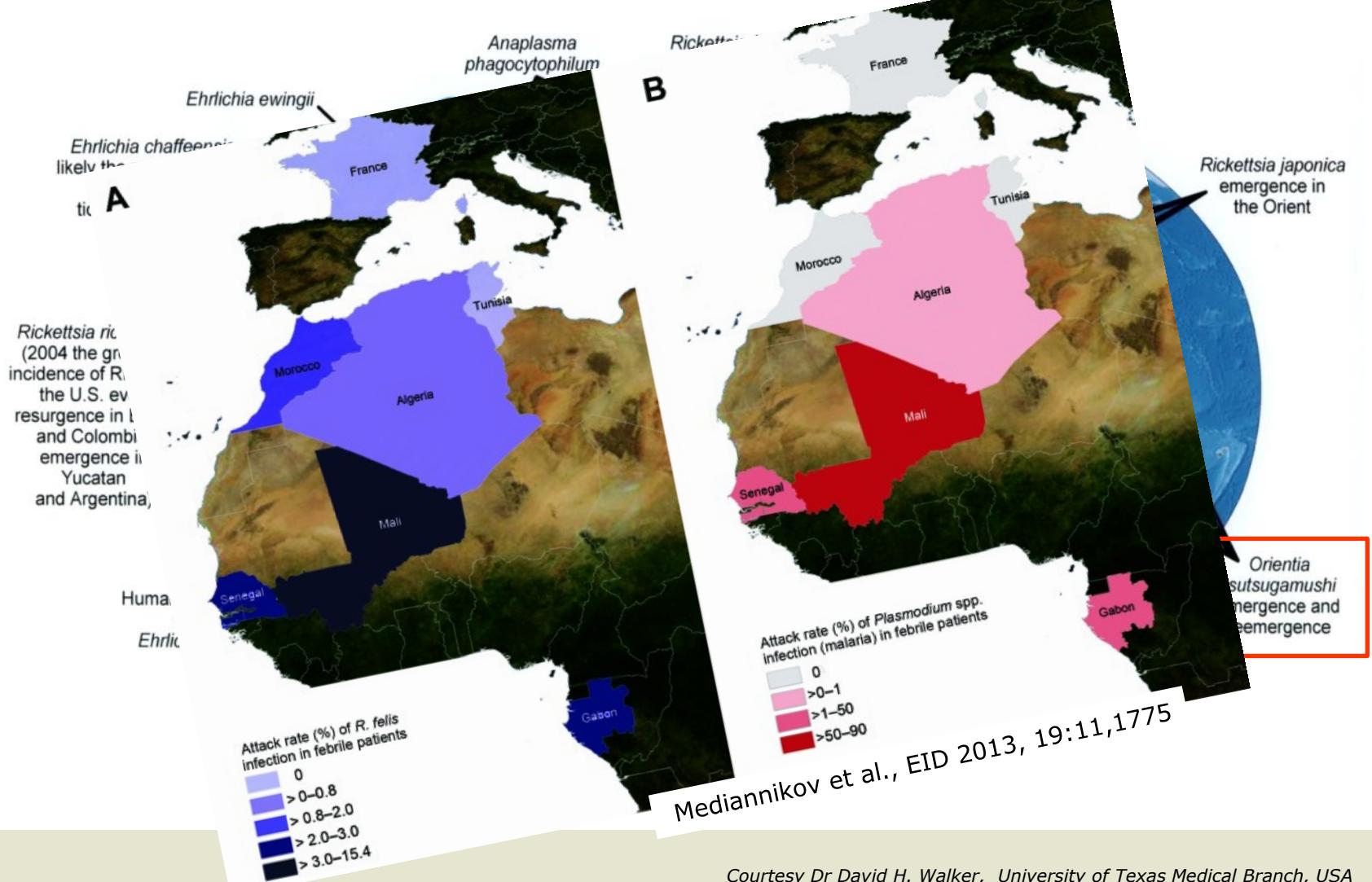
**Kato-like
TA, Japan**

Universidad del Desarrollo, Santiago, Chile
 Pontificia Universidad Católica de Chile, Santiago, Chile
 MORU and LOMWRU - diagnostics

Rickettsial infections and scrub typhus



Rickettsial infections and scrub typhus





Rickettsial infections and

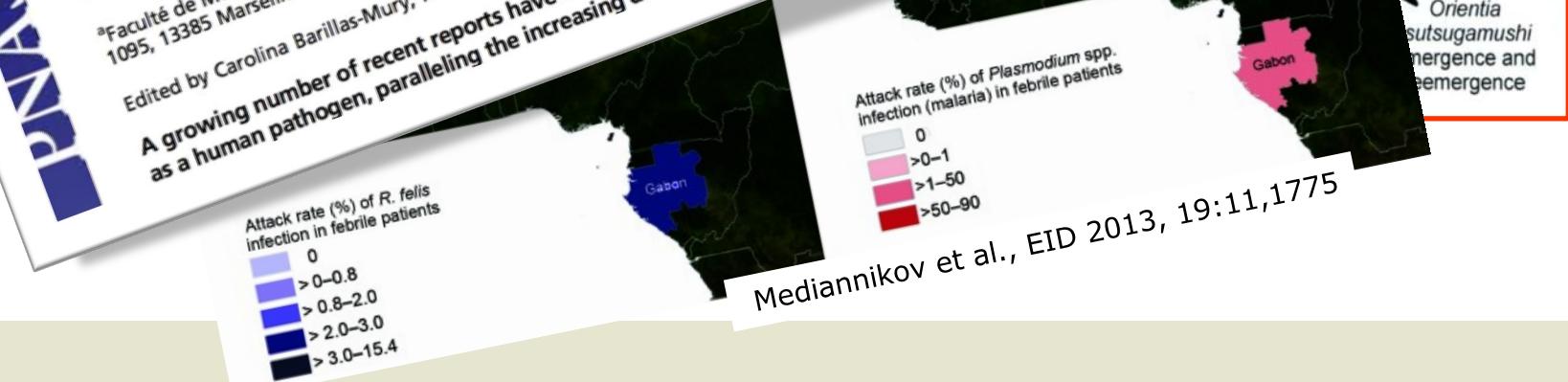
Transmission potential of Rickettsia felis infection by Anopheles gambiae mosquitoes

Constantin Dieme^{a,b,1}, Yassina Bechah^{a,1}, Cristina Socolovschi^a, Gilles Audoly^a, Jean-Michel Berenger^a, Ousmane Faye^b, Didier Raoult^a, and Philippe Parola^{a,2}

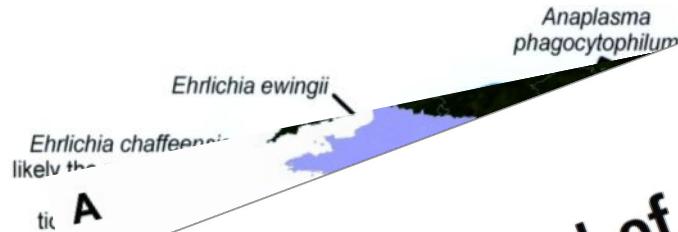
^aFaculté de Médecine, Aix Marseille Université, Unité de Recherche sur les Maladies Infectieuses Tropicales et Emergentes, UM63, CNRS 7278, IRD 198, INSERM 1095, 13385 Marseille Cedex 5, France; and ^bLaboratoire d'Ecologie Vectorielle et Parasitaire, Université Cheikh Anta Diop de Dakar, BP 5005 Dakar, Senegal

Edited by Carolina Barillas-Mury, National Institutes of Health, Bethesda, MD, and approved May 1, 2015 (received for review July 21, 2014)

A growing number of recent reports have implicated Rickettsia felis as a human pathogen, paralleling the increasing detection of R. felis



Mediannikov et al., EID 2013, 19:11,1775



CrossMark
click for updates



Rickettsial infections and

Transmission potential of Rickettsia felis infection by Anopheles gambiae mosquitoes

Constantin Dieme^{a,b,1}, Yassina Bechah^{a,1}, Cristina Socolovschi^{a,2}, Didier Raoult^a, and Philippe Parola^{a,2}

^aFaculté de Médecine, Aix Marseille Université, 1095, 13385 Marseille Cedex 15, France

Edited by Caroline

A growing num
as a human path

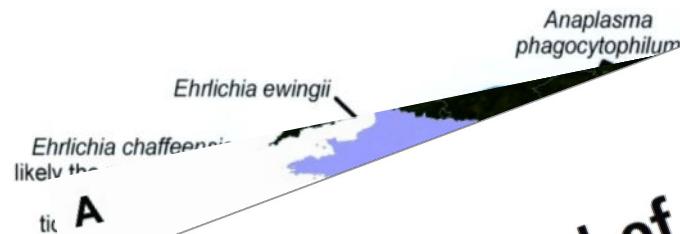
Attack rate (%) of
infection in febrile

- 0
- >0-0.8
- >0.8-2.0
- >2.0-3.0
- >3.0-15.4

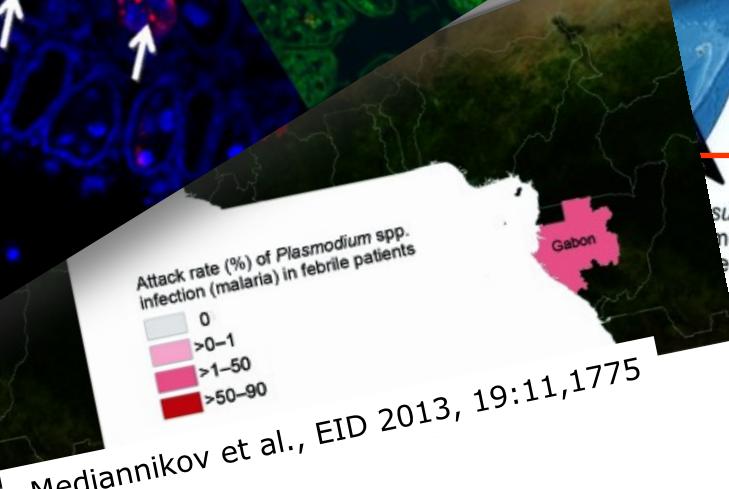
Attack rate (%) of Plasmodium spp.
infection (malaria) in febrile patients

- 0
- >0-1
- >1-50
- >50-90

Mediannikov et al., EID 2013, 19:11,1775



click for updates



Orientia
tsutsugamushi
emergence and
reemergence



LETTER

R Leeches as further potential vectors for rickettsial infections

We were very interested in the discovery and comprehensive investigation by Dieme et al. (1) of mosquitoes as potential vectors for *Rickettsia felis*. We would like to draw attention to another ectoparasite that we encountered as a possibly overlooked potential

Travelling Anoplites

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Edited by Caroline E. O'Neill

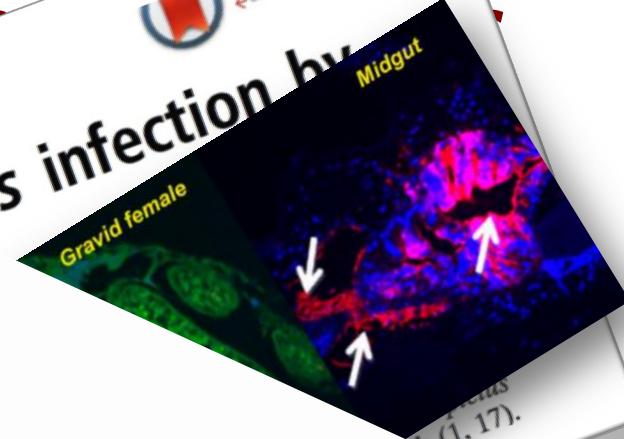
A growing number of leeches as a human pathogen

Leeches as a vector as a human pathogen in Africa, Asia, and Europe

Leeches as a vector as a human pathogen in Africa, Asia, and Europe

Infections and

R felis infection by



household survey in the patient's village in 2010, 146 (75.3%) of 194 villagers aged ≥15 y reported that they had been bitten by leeches in the previous year. Leech bites were associated in multivariate analysis with being a farmer and younger age (both

clarify the role of leeches as potential vectors for infectious diseases.

Günther Slesak^{a,1}, Saythong Inthalath^b, Sabine Dittrich^{c,d}, Daniel H. Paris^{c,d}, and Paul N. Newton^{c,d}

^aRickettsia africae throughout sub-Saharan Africa

^bCentre for Clinical Research and Education in Australia

Q:6

67. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 701–706.
68. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 707–711.
69. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 713–717.
70. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 719–723.
71. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 725–729.
72. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 731–735.
73. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 737–741.
74. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 743–747.
75. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 749–753.
76. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 755–759.
77. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 761–765.
78. Ushijima, T., et al. 2006. *Int J Parasitol* 36: 767–771.



LETTER

R₁₂ Leeches as further potential vectors for rickettsial infections

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Trapping Anoplites

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Edited by Caroline M. Sazani
A growing number of rickettsiae as a human pathogen



Leeches as a vector as a human pathogen

Rickettsia through sub-Saharan Africa



Eschar lesion after leech-bite, PCR / DNA seq.
Rickettsia felis

Rickettsia felis infection by leeches



Midgut



Ri
LETTERLeeches
rickettsiae

VECTOR-BORNE AND ZOONOTIC DISEASES
Volume 16, Number 4, 2016
Mary Ann Liebert, Inc.
DOI: 10.1089/vbz.2015.1849

Molecular Detection of Zoonotic Rickettsiae and Anaplasma spp. in Domestic Dogs and Their Ectoparasites in Bushbuckridge, South Africa

O. tsutsugamushi-like
16S rRNA
96.1% homology



Constantine
Didier Raoult

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1095, 13385 Marseille Cedex 5, France

Edited by Carolina Barillas-Mury, National

A growing number of recent reports have
as a human pathogen, paralleling the increa

Rickettsia parkeri
every as a human
pathogen

Rickettsia prowazekii*
reemergence in Burundi,
Algeria, Peru, and Europe

Rickettsia
through
sub-Saharan

Why are “tropical” Rickettsial diseases important ?

Leading causes of treatable undifferentiated febrile illness (SEA)

Highly endemic in SEA (elsewhere?)

Potentially severe, substantial economical impact (DALYs)

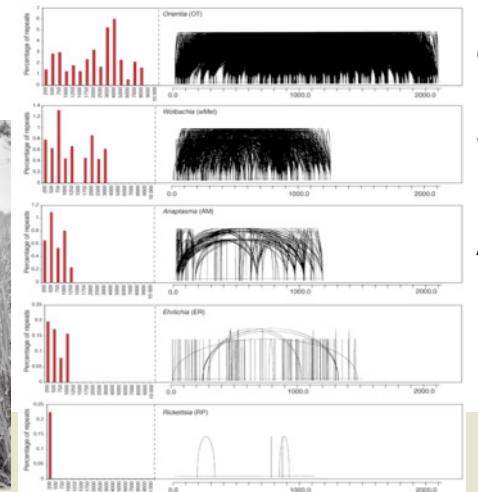
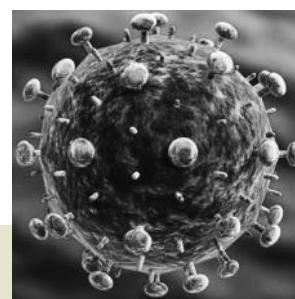
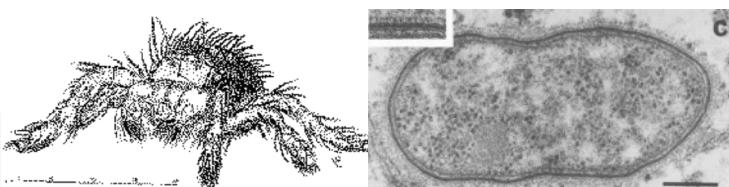
Scrub typhus – short duration of immune protection (transience)

Treatment without impact on incidence reduction (humans = dead end hosts)!

WHO 1999:

“Scrub typhus is probably one of the most under diagnosed and underreported febrile illnesses requiring hospitalization in the region”

Highly interesting diseases!



Thank you for your attention!



trapping rodents and chigger mites at dusk, Laos 2015