Rickettsiosis

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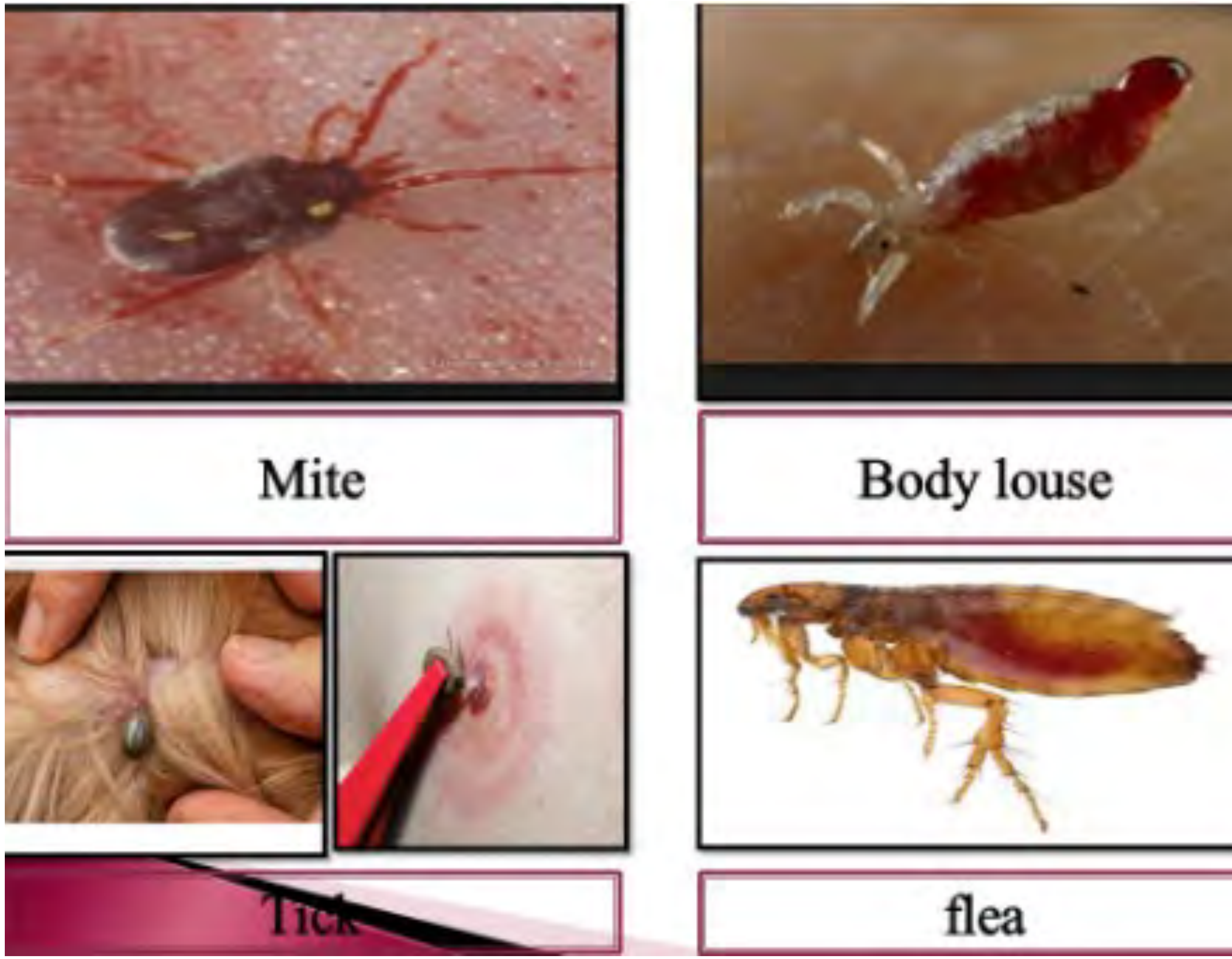
- NO CONFLICTS OF INTEREST TO DECLARE

Outline

- **Rickettsial infections**

- Epidemiology
- Classification
- Pathogenesis
- Clinical manifestations
- Complications
- Diagnosis
- Treatment
- Prevention



Meta-Analysis > J Travel Med. 2020 Dec 23;27(8):taaa207. doi: 10.1093/jtm/taaa207.

Aetiology of fever in returning travellers and migrants: a systematic review and meta-analysis

- Tropical infections accounted for 33% of fever diagnoses
- Febrile cases among tourists were (58%, 21-88%), followed by VFRs (15%, 7-21%), business/research/volunteers (14%, 11- 23%) and migrants (6%, 2-60%)
- Duration from travel and presentation was 13 days (median 7)
- Most travelled for < 30 days (62%, 60-74%), took inadequate malaria chemoprophylaxis (73%, 41-83%), or received any pre-travel medical advice (52%, 9-73%)
- Malaria causing fever 71%, dengue 16 % and enteric fever 7% and **rickettsioses 5% among all tropical diseases**

Tropical Medicine and Infectious Disease

Trop Med Infect Dis. 2022 Feb; 7(2): 18.

MDPI

Review

Rickettsiosis in Southeast Asia: Summary for International Travellers during the COVID-19 Pandemic

- >450 travel related rickettsioses reported worldwide
- *R.typhi* and *O.tsutsugamushi* common
- Scrub typhus most common cause of febrile illness in Thailand, Vietnam, Malaysia and India
- **Among GeoSentinel network, 0.6% had rickettsioses: Spotted fever was found in Sub-Saharan Africa (82%), >50% had scrub typhus in SEA, murine typhus in Bali**
- Serology cross reacts with other bacteria such as *Anaplasma* and *Ehrlichia* spp

TABLE I Biogroups of Rickettsiaceae(12)

Biogroup	Disease	Vector	Host	Organism
Spotted fever	Rocky Mountain spotted fever (RMSF)	tick	dogs, rodents	*Rickettsia rickettsii*
	Rickettsialpox	mite	mice	*Rickettsia akari*
	Indian tick typhus / Boutonneuse fever/ Mediterranean spotted fever (MSF)	tick	dogs, rodents	*Rickettsia conorii*
Typhus	Epidemic louse borne typhus	louse	human	*Rickettsia prowazekii*
	Brill-Zinsser disease (recrudescent typhus)	louse	human	*Rickettsia prowazekii*
	Endemic/Murine flea borne typhus	flea	rats	*Rickettsia typhi*
Scrub typhus	Scrub typhus	chigger	rodents	*Orientia tsutsugamushi*
Miscellaneous	Ehrlichioses and Anaplasmosis	tick	deer,dogs,rodents	*Ehrlichia , Anaplasma*
	TIBOLA (tick borne lymphadenopathy)	tick	wild boar	*Rickettsia slovaca*
	DEBONEL	tick	wild boar	*Rickettsia slovaca*

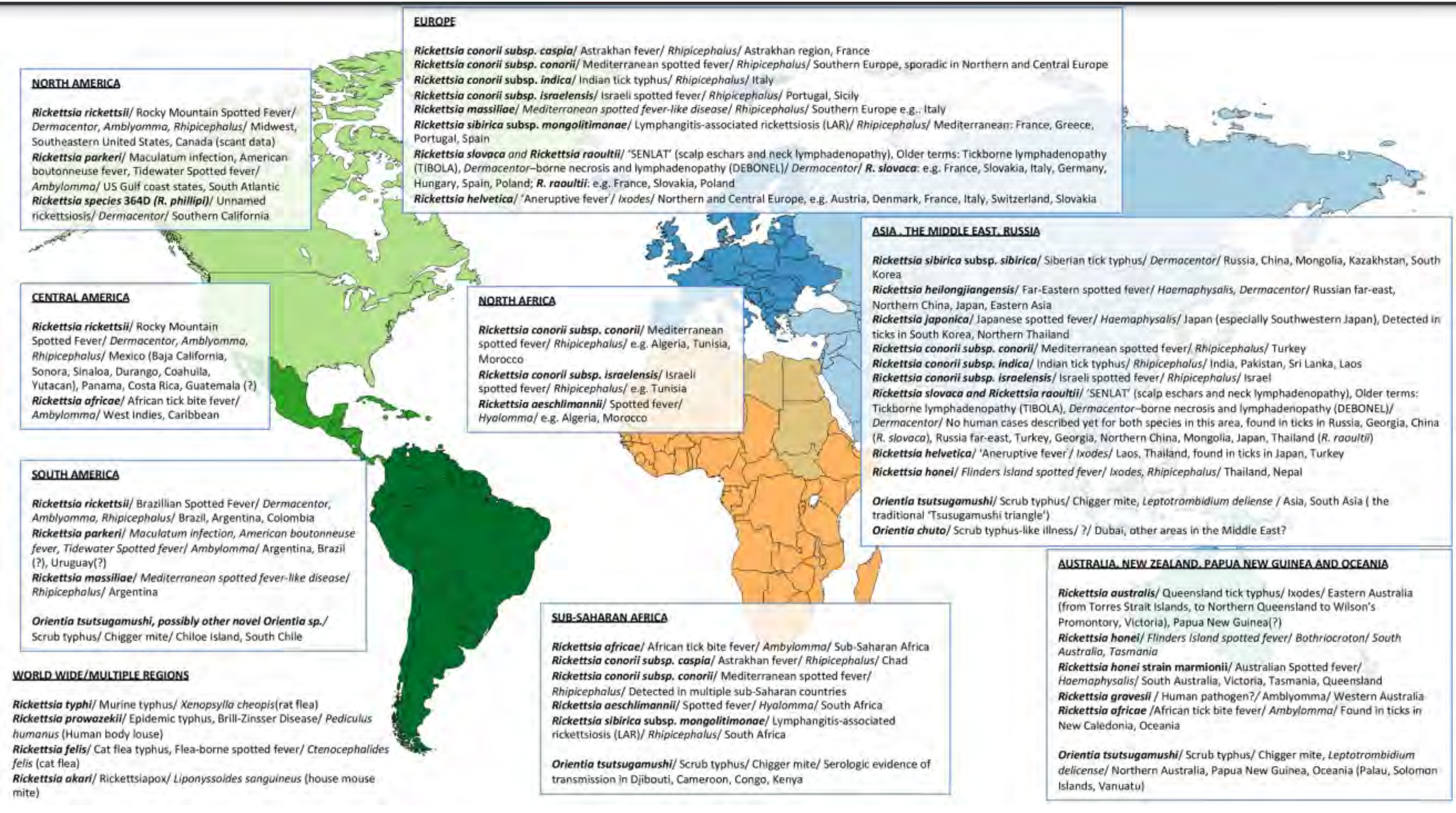
DEBONEL: Dermacentor borne necrosis-eschar-lymphadenopathy.

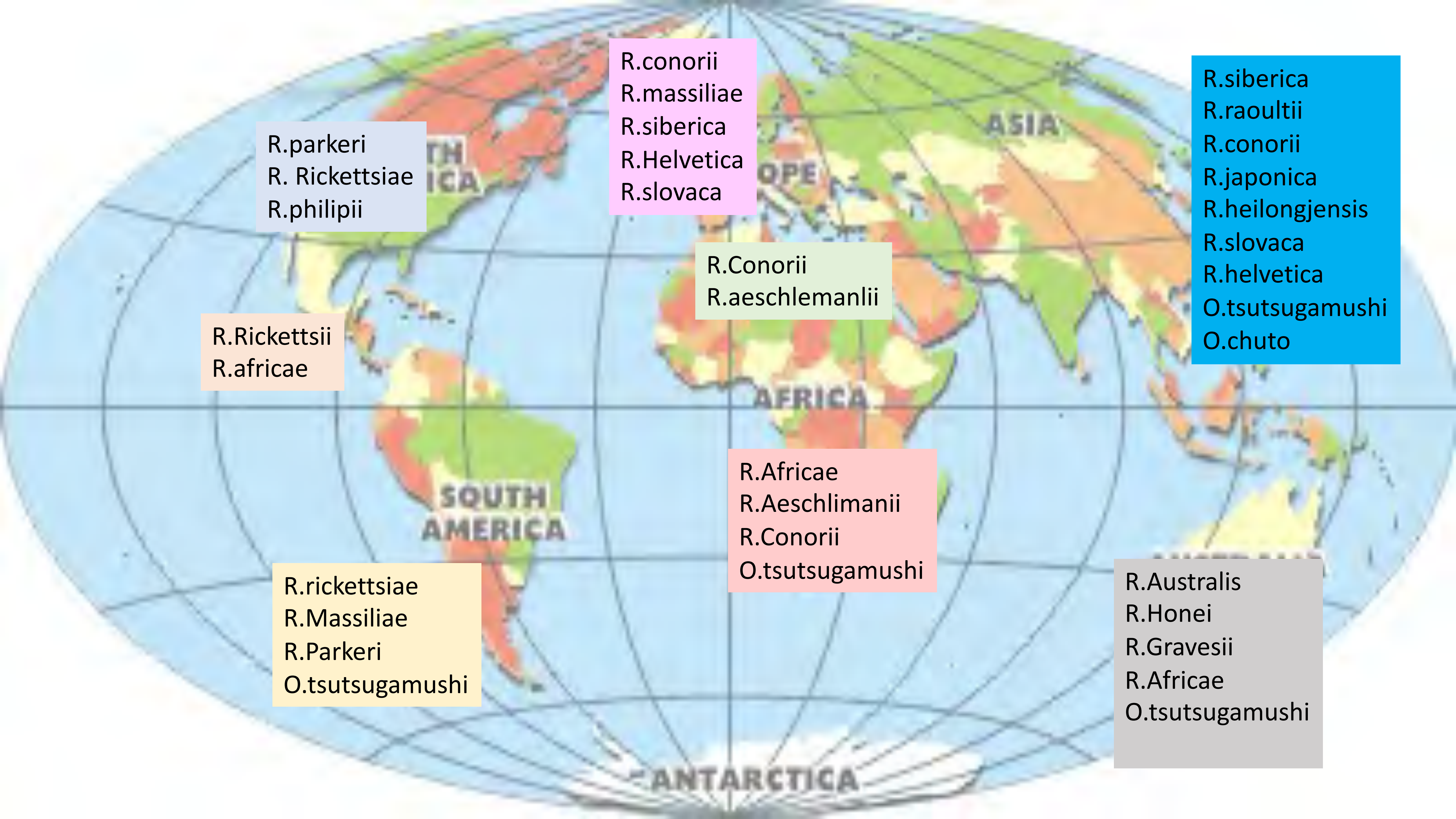
USA

USA, Russia, Korea

India, Kenya, Mediterrean

Asia, Africa, Central & South America


EUROPE
Rickettsia conorii subsp. caspia/ Astrakhan fever/ Rhipicephalus/ Astrakhan region, France
Rickettsia conorii subsp. conorii/ Mediterranean spotted fever/ Rhipicephalus/ Southern Europe, sporadic in Northern and Central Europe
Rickettsia conorii subsp. indica/ Indian tick typhus/ Rhipicephalus/ Italy
Rickettsia conorii subsp. israelensis/ Israeli spotted fever/ Rhipicephalus/ Portugal, Sicily
Rickettsia massiliae/ Mediterranean spotted fever-like disease/ Rhipicephalus/ Southern Europe e.g. Italy
Rickettsia sibirica subsp. mongolitimonae/ Lymphangitis-associated rickettsiosis (LAR)/ Rhipicephalus/ Mediterranean: France, Greece, Portugal, Spain
Rickettsia slovaca and Rickettsia raoultii/ 'SENLAT' (scalp eschars and neck lymphadenopathy), Older terms: Tickborne lymphadenopathy (TIBOLA), Dermacentor–borne necrosis and lymphadenopathy (DEBONEL)/ Dermacentor/ R. slovaca: e.g. France, Slovakia, Italy, Germany, Hungary, Spain, Poland; R. raoultii: e.g. France, Slovakia, Poland
Rickettsia helvetica/ 'Aneruptive fever'/ Ixodes/ Northern and Central Europe, e.g. Austria, Denmark, France, Italy, Switzerland, Slovakia
NORTH AMERICA
Rickettsia rickettsii/ Rocky Mountain Spotted Fever/ Dermacentor, Amblyomma, Rhipicephalus/ Midwest, Southeastern United States, Canada (scant data)
Rickettsia parkeri/ Maculatum infection, American boutonneuse fever, Tidewater Spotted fever/ Ambylomma/ US Gulf coast states, South Atlantic
Rickettsia species 364D (R. phillipi)/ Unnamed rickettsiosis/ Dermacentor/ Southern California
CENTRAL AMERICA
Rickettsia rickettsii/ Rocky Mountain Spotted Fever/ Dermacentor, Amblyomma, Rhipicephalus/ Mexico (Baja California, Sonora, Sinaloa, Durango, Coahuila, Yutacan), Panama, Costa Rica, Guatemala (?)
Rickettsia africae/ African tick bite fever/ Ambylomma/ West Indies, Caribbean
NORTH AFRICA
Rickettsia conorii subsp. conorii/ Mediterranean spotted fever/ Rhipicephalus/ e.g. Algeria, Tunisia, Morocco
Rickettsia conorii subsp. israelensis/ Israeli spotted fever/ Rhipicephalus/ e.g. Tunisia
Rickettsia aeschlimannii/ Spotted fever/ Hyalomma/ e.g. Algeria, Morocco
ASIA , THE MIDDLE EAST, RUSSIA
Rickettsia sibirica subsp. sibirica/ Siberian tick typhus/ Dermacentor/ Russia, China, Mongolia, Kazakhstan, South Korea
Rickettsia heilongjiangensis/ Far-Eastern spotted fever/ Haemaphysalis, Dermacentor/ Russian far-east, Northern China, Japan, Eastern Asia
Rickettsia japonica/ Japanese spotted fever/ Haemaphysalis/ Japan (especially Southwestern Japan), Detected in ticks in South Korea, Northern Thailand
Rickettsia conorii subsp. conorii/ Mediterranean spotted fever/ Rhipicephalus/ Turkey
Rickettsia conorii subsp. indica/ Indian tick typhus/ Rhipicephalus/ India, Pakistan, Sri Lanka, Laos
Rickettsia conorii subsp. israelensis/ Israeli spotted fever/ Rhipicephalus/ Israel
Rickettsia slovaca and Rickettsia raoultii/ 'SENLAT' (scalp eschars and neck lymphadenopathy), Older terms: Tickborne lymphadenopathy (TIBOLA), Dermacentor–borne necrosis and lymphadenopathy (DEBONEL)/ Dermacentor/ No human cases described yet for both species in this area, found in ticks in Russia, Georgia, China (R. slovaca), Russia far-east, Turkey, Georgia, Northern China, Mongolia, Japan, Thailand (R. raoultii)
Rickettsia helvetica/ 'Aneruptive fever'/ Ixodes/ Laos, Thailand, found in ticks in Japan, Turkey
Rickettsia honei/ Flinders Island spotted fever/ Ixodes, Rhipicephalus/ Thailand, Nepal
Orientia tsutsugamushi/ Scrub typhus/ Chigger mite, Leptotrombidium deliense / Asia, South Asia (the traditional 'Tsusugamushi triangle')
Orientia chuto/ Scrub typhus-like illness/ ?/ Dubai, other areas in the Middle East?
SOUTH AMERICA
Rickettsia rickettsii/ Brazillian Spotted Fever/ Dermacentor, Amblyomma, Rhipicephalus/ Brazil, Argentina, Colombia
Rickettsia parkeri/ Maculatum infection, American boutonneuse fever, Tidewater Spotted fever/ Ambylomma/ Argentina, Brazil (?), Uruguay(?)
Rickettsia massiliae/ Mediterranean spotted fever-like disease/ Rhipicephalus/ Argentina
Orientia tsutsugamushi, possibly other novel Orientia sp./ Scrub typhus/ Chigger mite/ Chiloe Island, South Chile
AUSTRALIA, NEW ZEALAND, PAPUA NEW GUINEA AND OCEANIA
Rickettsia australis/ Queensland tick typhus/ Ixodes/ Eastern Australia (from Torres Strait Islands, to Northern Queensland to Wilson's Promontory, Victoria), Papua New Guinea(?)
Rickettsia honei/ Flinders Island spotted fever/ Bothriocroton/ South Australia, Tasmania
Rickettsia honei strain marmionii/ Australian Spotted fever/ Haemaphysalis/ South Australia, Victoria, Tasmania, Queensland
Rickettsia gravesii / Human pathogen?/ Amblyomma/ Western Australia
Rickettsia africae /African tick bite fever/ Ambylomma/ Found in ticks in New Caledonia, Oceania
Orientia tsutsugamushi/ Scrub typhus/ Chigger mite, Leptotrombidium delicense/ Northern Australia, Papua New Guinea, Oceania (Palau, Solomon Islands, Vanuatu)
WORLD WIDE/MULTIPLE REGIONS
Rickettsia typhi/ Murine typhus/ Xenopsylla cheopis(rat flea)
Rickettsia prowazekii/ Epidemic typhus, Brill-Zinsser Disease/ Pediculus humanus (Human body louse)
Rickettsia felis/ Cat flea typhus, Flea-borne spotted fever/ Ctenocephalides felis (cat flea)
Rickettsia akari/ Rickettsiapox/ Liponyssoides sanguineus (house mouse mite)
SUB-SAHARAN AFRICA
Rickettsia africae/ African tick bite fever/ Ambylomma/ Sub-Saharan Africa
Rickettsia conorii subsp. caspia/ Astrakhan fever/ Rhipicephalus/ Chad
Rickettsia conorii subsp. conorii/ Mediterranean spotted fever/ Rhipicephalus/ Detected in multiple sub-Saharan countries
Rickettsia aeschlimannii/ Spotted fever/ Hyalomma/ South Africa
Rickettsia sibirica subsp. mongolitimonae/ Lymphangitis-associated rickettsiosis (LAR)/ Rhipicephalus/ South Africa
Orientia tsutsugamushi/ Scrub typhus/ Chigger mite/ Serologic evidence of transmission in Djibouti, Cameroon, Congo, Kenya



R.parkeri
R. Rickettsiae
R.philipii
R.conorii
R.massiliae
R.siberica
R.Helvetica
R.slovaca
R.siberica
R.raoultii
R.conorii
R.japonica
R.heilongjensis
R.slovaca
R.helvetica
O.tsutsugamushi
O.chuto
ASIA
R.Conorii
R.aeschlemanlii
R.Rickettsii
R.africae
AFRICA
SOUTH AMERICA
R.Africae
R.Aeschlimanii
R.Conorii
O.tsutsugamushi
R.rickettsiae
R.Massiliae
R.Parkeri
O.tsutsugamushi
R.Australis
R.Honei
R.Gravesii
R.Africae
O.tsutsugamushi
ANTARCTICA

Select spotted fever group rickettsiae

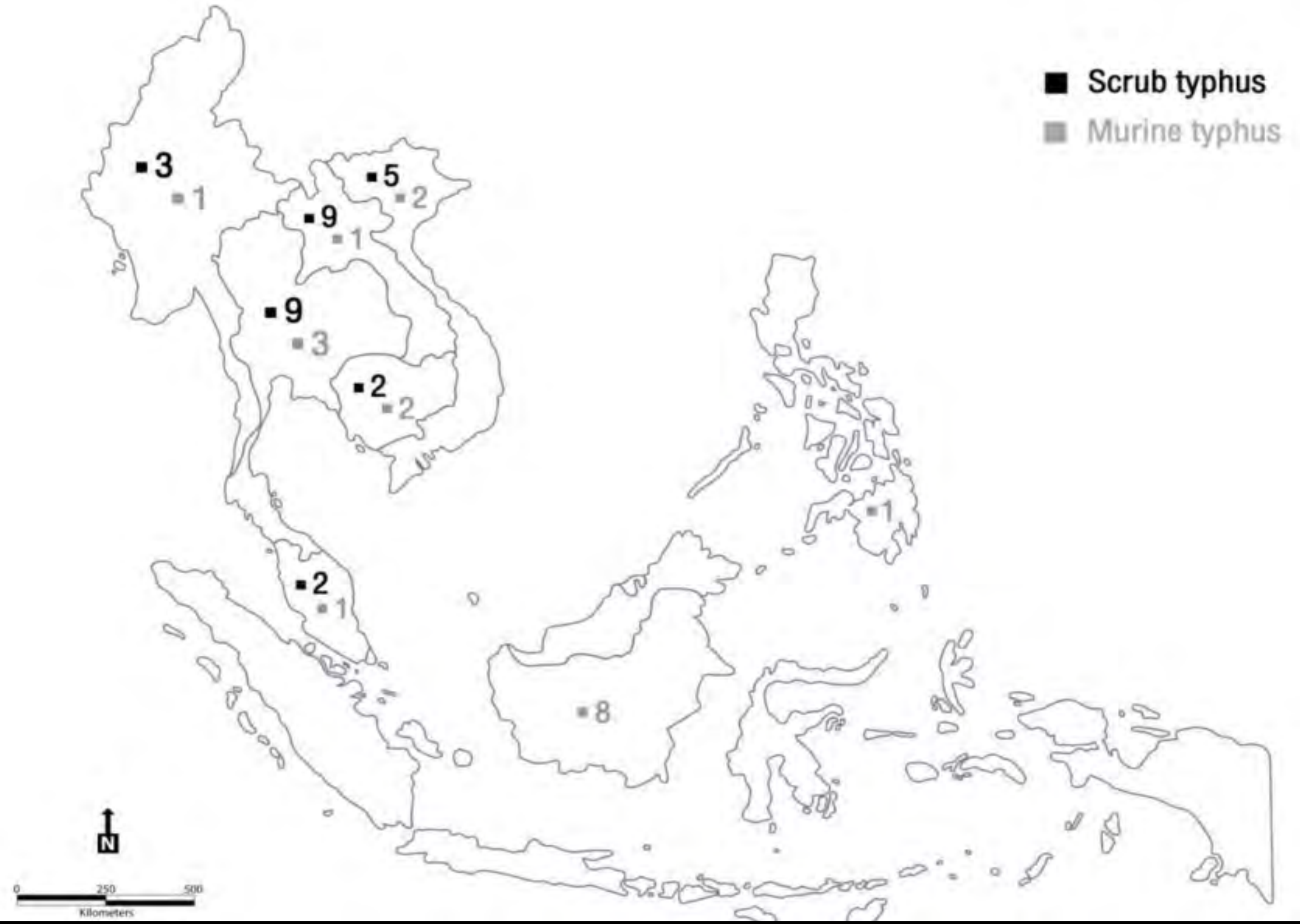
Disease	Organism	Vectors	Geographic distribution	Severity of symptoms
African tick bite fever	*Rickettsia africae*	*Amblyomma* ticks	Sub-Saharan Africa Caribbean	Mild
Flea rickettsiosis	*R. felis*	Cat fleas Mosquitos	Europe North America South America Africa Asia	Mild
Flinders Island spotted fever	*R. honei*	Ticks of several genera	Australia Southeast Asia Thailand	Mild to moderate
Japanese spotted fever	*R. japonica*	*Dermacentor* *Haemaphysalis* *Ixodes* ticks	Southwest Japan Thailand Korea	Mild to severe
Lymphangitis-associated rickettsiosis	*R. sibirica mongolotimonae*	*Hyalomma* ticks	China Sub-Saharan Africa France	Mild to moderate
Mediterranean spotted fever	*R. conorii*	*R. sanguineous* *Haemaphysalis* ticks	North Africa Kenya Israel Southern and Eastern Europe Pakistan	Mild to severe
Queensland tick typhus	*R. australis*	*Ixodes* ticks	Eastern Australia	Mild to moderate
Rickettsialpox	*R. akari*	*Allodermanyssus sanguineous* (mouse mites)	North America Korea Balkans	Mild
Rocky mountain spotted fever	*R. rickettsii*	*Dermacentor andersoni* *Dermacentor variabilis* *Rhipicephalus sanguineous* ticks *Ambylomma* ticks	United States Southern Canada Mexico Central America Brazil	Human – severe to mild
R. parkeri infection	*R. parkeri*	*Amblyomma* ticks	United States Brazil Uruguay Central America	–
Siberian tick typhus	*R. sibirica, R. sibirica mongolotimonae*	*Dermacentor* ticks	China Russia Pakistan Central Asia Southern and Eastern Europe	Mild to moderate
Tick-borne lymphadenopathy	*R. slovaca*	*Dermacentor* ticks	Europe	Mild

TICK BORNE RICKETTSIOSES

International Journal of Infectious Diseases. 28. 126-139.

Map showing the distribution of the main human tick-borne rickettsioses.

Reported scrub and murine typhus in SEA



Epidemiology

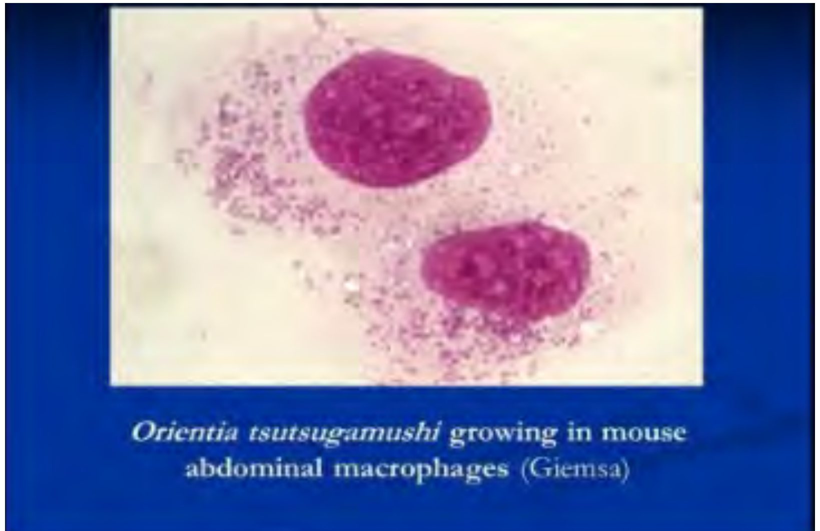
- Family Rickettsiaceae; Genera Rickettsia and Orientia
- Genus Rickettsia has 31 species
- Two main groups, the spotted fever group (SFG) and the typhus group (TG)
- Typhus group: R.prowazekii and R.typhi
- *Rickettsia tsutsugamushi* was renamed *Orientia tsutsugamushi*; *Rickettsia burnetii*, renamed *Coxiella burnetiid*
- Found globally with regional specificity
- Vectors: Fleas – R.felis, R.typhi; Mites – R.akari; Lice-R.prowazekii; Ticks: Cause spotted fever (SFG)

Organism

Rickettsial infections can be classified into

- Spotted fever group : 4 subgroup
- Typhus group
- Scrub typhus

Immunity is strain dependent

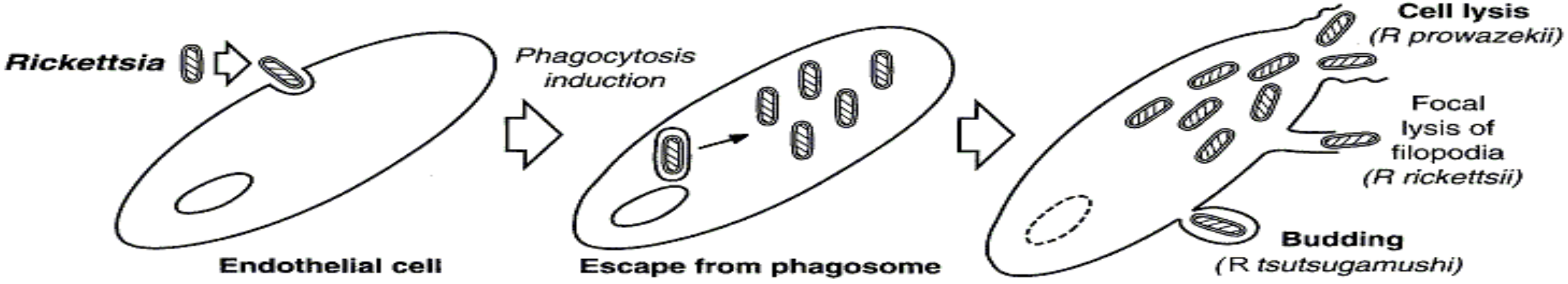


Orientia tsutsugamushi growing in mouse abdominal macrophages (Giemsa)

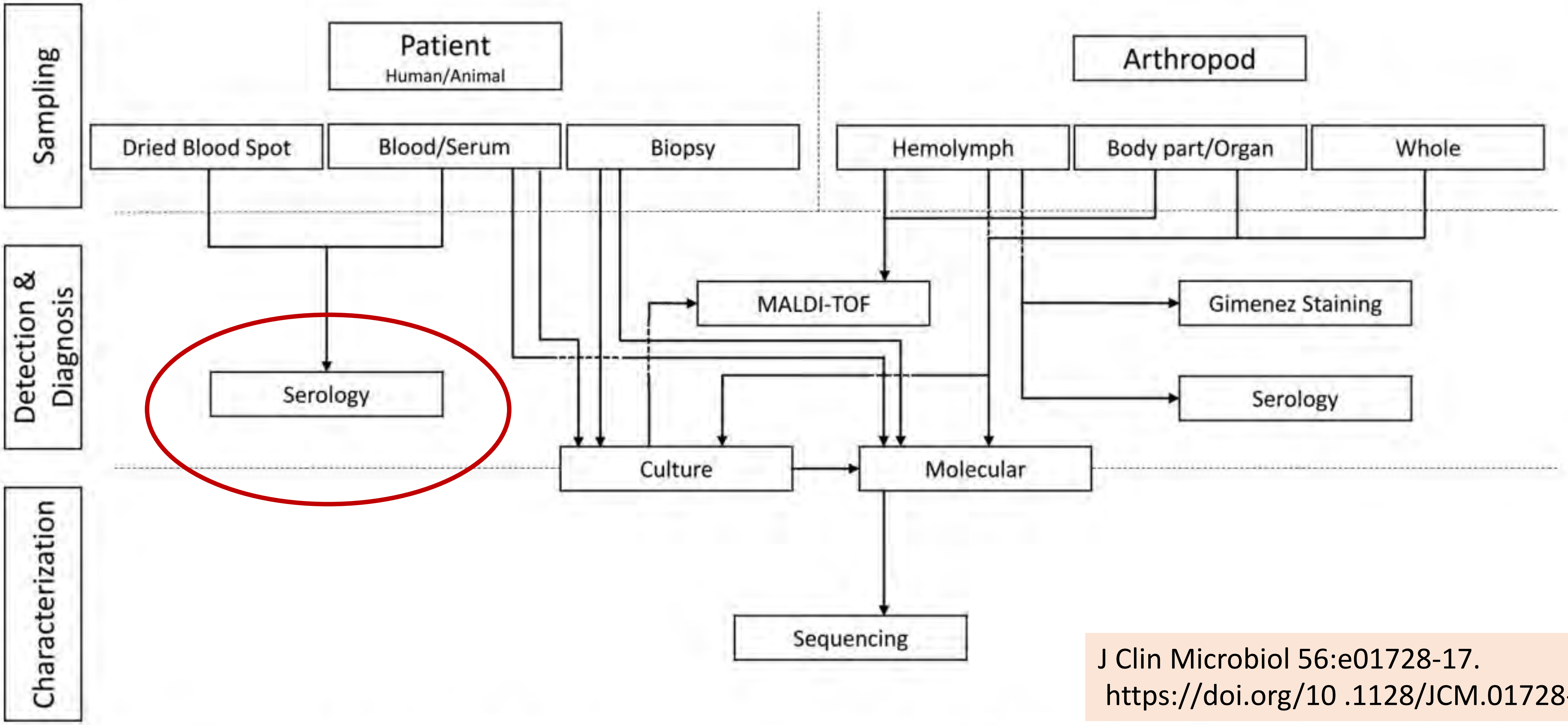
- ***Scrub typhus***: *Orientia Tsutsugamushi :* **antigenic heterogeneity > 20 distinct strains**
  - *Karp*
  - Gilliam
  - Kato
  - Shimokoshi
  - Kawasaki
  - Kuroki
- *Orientia Chuto* – Middle east

Pathogenesis and Immunity

- Predominantly infects endothelial cells causing vasculitis
  - Multi-focal areas of endothelial injury and blood vessel damage
  - Leakage of blood into tissues (rash & edema)
  - Organ and tissue damage
- Increased endothelial and macrophage markers are associated with disease severity



Ref:Rajapakse S, Rodrigo C, Fernando D. Scrub typhus: pathophysiology, clinical manifestations and prognosis. Asian Pacific journal of tropical medicine. 2012 Apr 1;5(4):261-4.



J Clin Microbiol 56:e01728-17.
https://doi.org/10 .1128/JCM.01728-17.

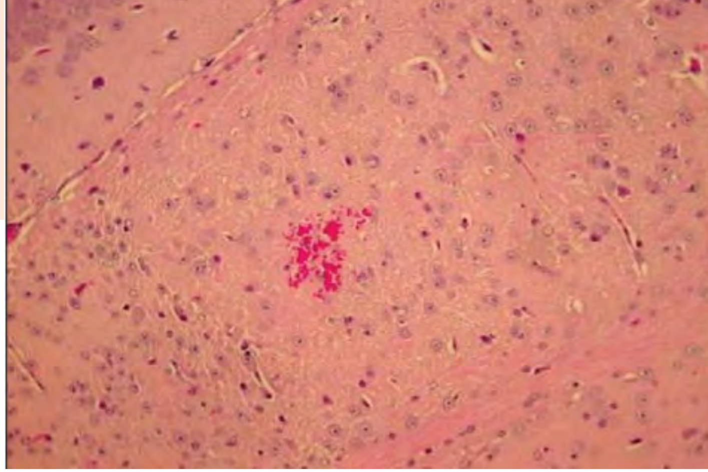
FIG 2 Illustration summarizing samples that can be obtained from patients and invertebrates and the testing that can be conducted with respect to sample type.

Diagnosis

- Serologic detection of convalescent antibodies is the mainstay of diagnosis of rickettsial infection –

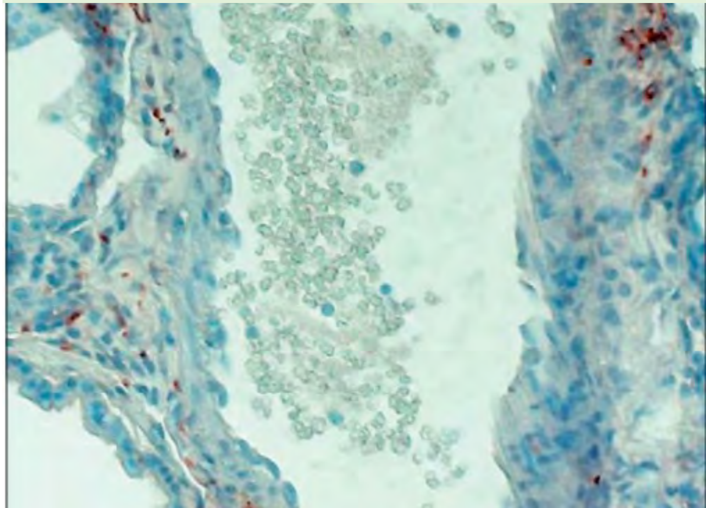
- Indirect immunofluorescence (IFA), Microimmunofluorescent (MIF) antibody test, Western blot immunoassay
- **Enzyme-linked immunosorbent assay (ELISA)**

- Immunologic detection in tissue: Eschars have large numbers of rickettsiae, biopsy of skin and other tissues (area of rash)
- PCR from blood, skin, tissue
- Isolation of rickettsia by inoculation into animals or cell cultures using fibroblast monolayers



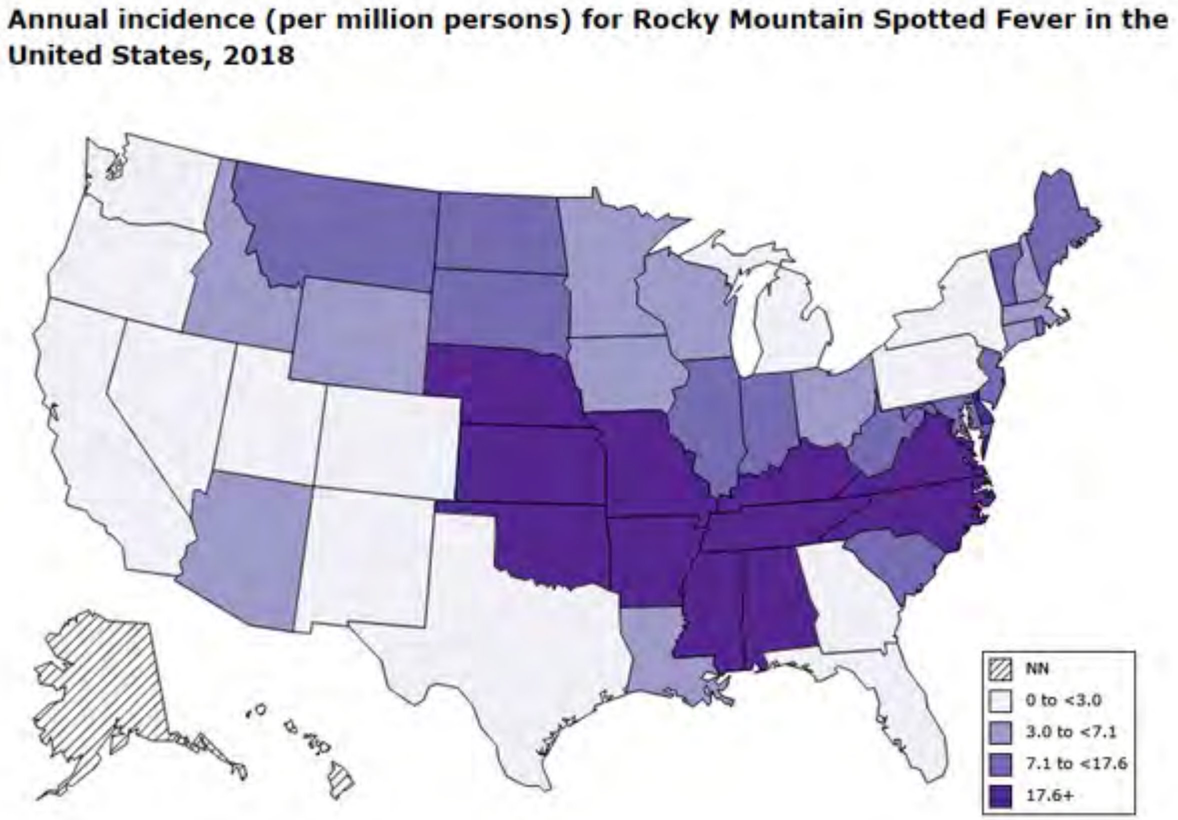
Brain infected with R.prowazekii

IHC of R.prowazekii in lungs



Rocky Mountain Spotted Fever

- First described by Howard Ricketts as an infection transmitted by ticks
- Gram negative obligate intracellular bacteria
- Tropic to vascular endothelium
- Vascular injury
- Vascular permeability
- Activation of clotting factors
- Host response leads to complications



- North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri) account for over 60% of RMSF cases

Epidemic typhus

- R.prowazekii
- Louse borne
- Epidemic typhus has caused more deaths than all the wars in history
- Rare
- Sylvatic cycle maintained by flying and their ectoparasites
- Recent epidemics in Burundi and Rwanda in jails or refugee camps
- Occur when hygiene is compromised in winters or spring
- Transmitted of bite sites by faeces or crushed lice
- Louse dies in a week if infected
- Looks red when infected
- Bioterrorism agent due to inhalation of aerosolized louse faeces

Typhos –smoky or hazy

Clinical features and diagnosis

- Severe myalgia, headache, fever, rash, arthralgia, abdominal pain
- Rash occurs only in 20-40% of cases and can be pleomorphic – erythematous, non confluent, macular, petechiae, purpura
- Delirium, coma and seizures in 80%
- Cough 38-70% of patients
- Brill-Zinsser: Re-activation years or decades after infection due to waning immunity

\- Continues to be reported

- Diagnosis is mainly by serology
- Rise in titres of specific Ab in acute and convalescent sera
- PCR: Real time PCR can differentiate from other SFG rickettsiae (gltA gene)
- Treat with Doxycycline or Chloramphenicol

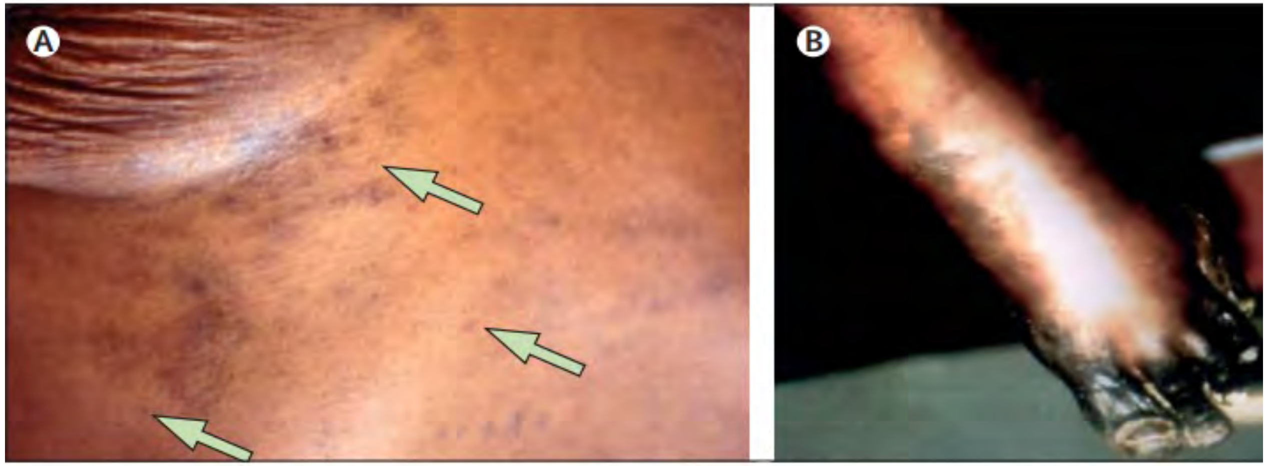


Figure 4: (A) Skin rash and (B) toe gangrene in a patient infected with epidemic typhus during Burundi outbreak, 1997

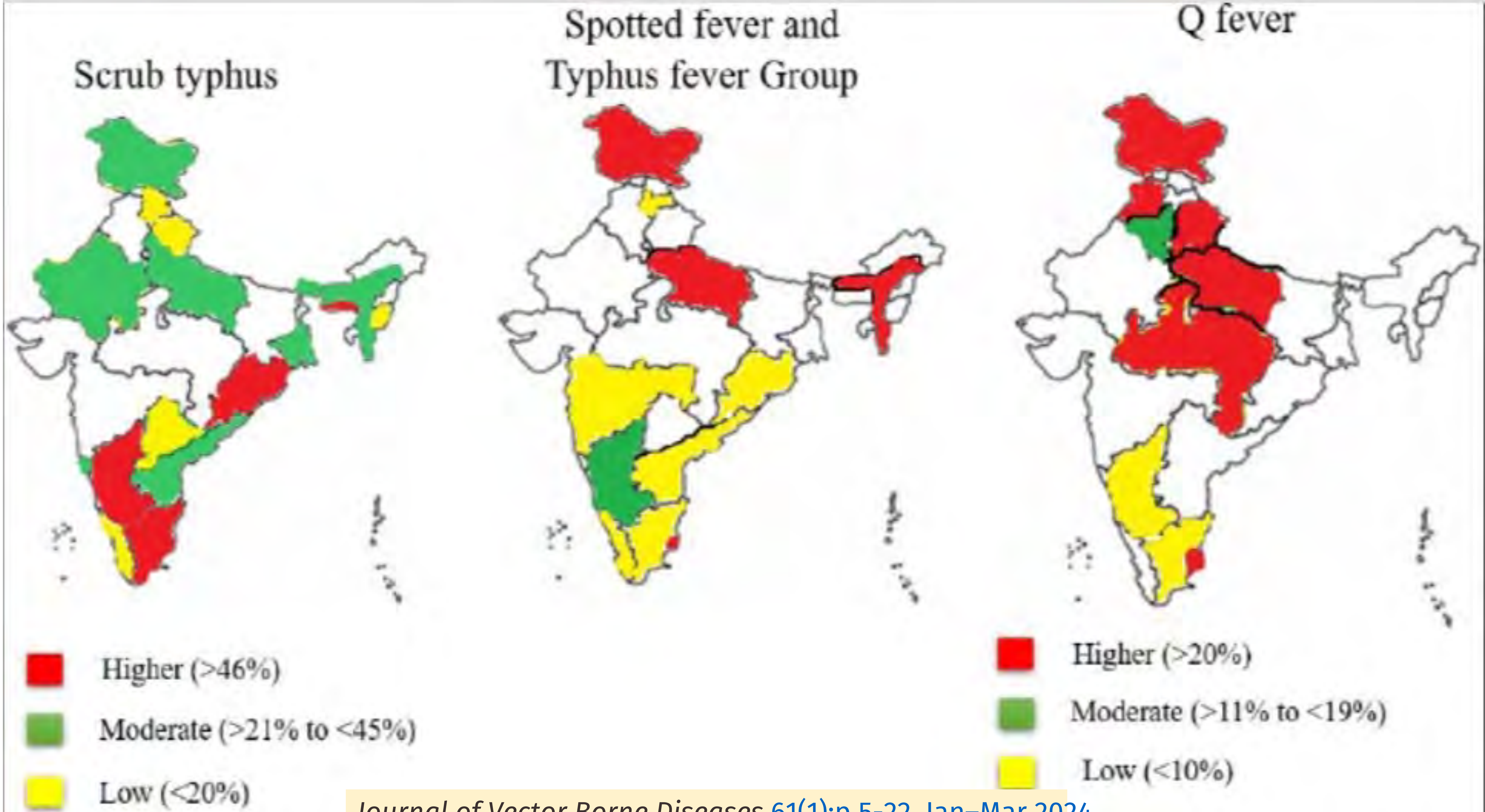
Trunk with a part of breast is shown in (A). Arrows show cutaneous eruptions.

Murine (endemic) Typhus

- Flea borne rickettsial illness caused by *Rickettsia typhi, R.felis and R.mooseri*
- Contact with infected flea faeces into cuts or scrapes of skin
- Fever, headache and rash 5-14 days after exposure
- Reported initially in India in a few states especially Jammu and Kashmir and then seroprevalence reported 1-2% in febrile patients in Vellore, Tamilnadu
- Diagnosis and treatment similar to scrub typhus

Indian tick typhus

- Caused by *R.conori*
- Synonyms: Kenya spotted fever, Mediterranean/Boutonneuse fever
- First described in India by Megaw who developed systemic symptoms after getting bit by a tick
- National Centre for Disease Control (NCDC) of India, conducted a serosurvey for five years (2005-2009) and recorded **27.5% of febrile patients positive against *R. conorii* antibodies**



Journal of Vector Borne Diseases 61(1):p 5-22, Jan–Mar 2024.

Orientia tsutsugamushi

Table 5. Current Known and Proposed Agents of Scrub Typhus.

Agent	Location
Orientia tsutsugamushi	Tsutsugamushi Triangle
Candidatus O. chuto	United Arab Emirates
Ca. O. chuto-like	Kenya
Candidatus O. chiloensis	Chile

- Obligate intracellular Gram-negative bacterium

-α-subdivision *Proteobacteria*

-order Rickettsiales

- family Rickettsiaceae

- Orientia –oriental
- Tsutsuga – illness or fever
- Mushi –insect or creature

Localized rickettsial infection may present as an eschar (“tache noir”) or rash at the site of arthropod inoculation

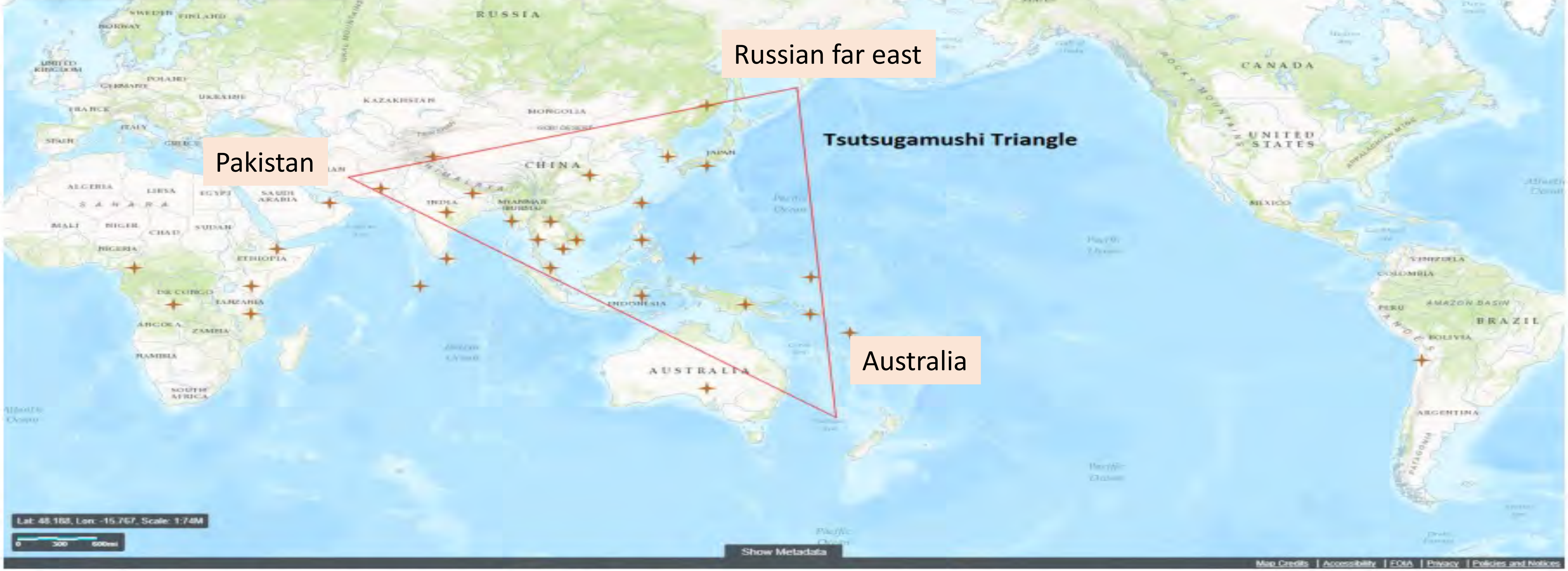


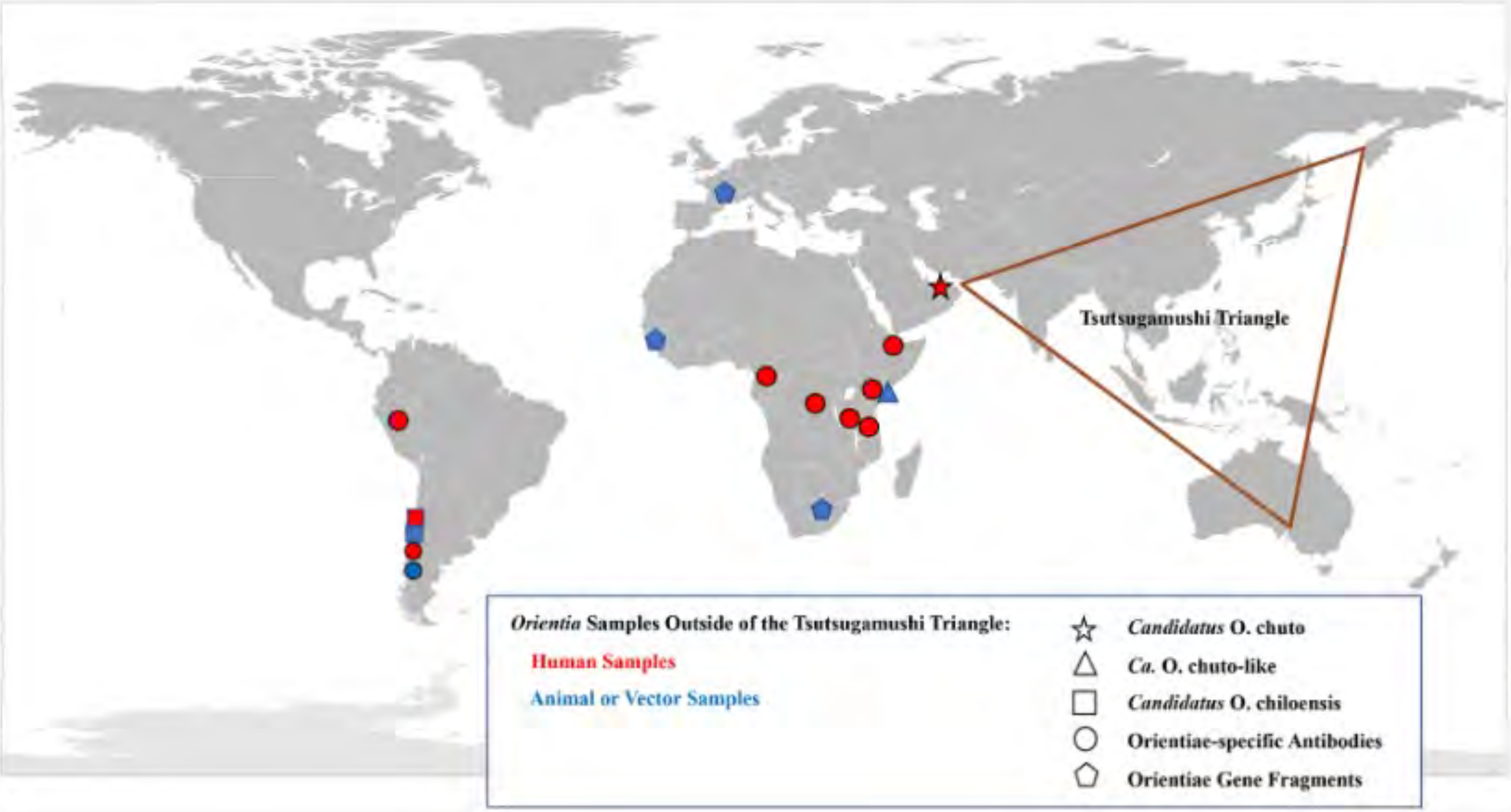
Fig 1. Worldwide map of countries with reported scrub typhus cases. The majority of scrub typhus cases occur in the "tsutsugamushi triangle" in the Asia-Pacific area. Countries with human cases are labeled with a star. [Modified from https://landsatlook.usgs.gov/viewer.html].

- Illness in 1 million/year but 1 billion at risk
- Most risk is in the "tsutsugamushi triangle"
- Outside this area: UAE (new strain-*O.chuto*), Chile (vector –leech), Africa (case reports in travelers)

Ref:Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM. A review of the global epidemiology of scrub typhus. PLoS neglected tropical diseases. 2017 Nov 3;11(11):e0006062.

Changing epidemiology of scrub typhus

Figure 2. Geographical Distribution of *Orientia* spp. and the Scrub Typhus: A Worldwide Disease.



Serological evidence found in

- Africa: Kenya, Djibouti
- South Africa
- South America: Chile, Iquitos
- Middle East

Cases reported from the Middle East, South America and Africa

RESEARCH ARTICLE

Estimating the burden of scrub typhus: A systematic review

Ana Bonell[1], Yoel Lubell[2,3], Paul N. Newton[3,4], John A. Crump[5], Daniel H. Paris[2,3,6,7]*

- Prospective studies report **incidence (median 4.6/100,000 highest in China** with 11.2/100,000/10 years)

- **Case fatality 12.2% and 13.6% for South India and northern Thailand, respectively**

- Median mortality: 6.0% in untreated & 1.4% in treated

- CNS involvement (13.6% mortality), multi-organ dysfunction (24.1% mortality)

PLOS NEGLECTED TROPICAL DISEASES

Table 1. Estimates of incidence and sero-prevalence per country.

First Author	Country	Incidence/ 100,000	Year data collected	Total number infected
Park	South Korea	17.7	2012	8,604
Yasunaga	Japan	3.6	2007–2008	210
Wu	China	1.22	2014	16,050
Lee	Taiwan	14.3	2000–2004	1,396
N/A	Thailand	11.8	2015	7,696
First Author	**Country, Region**	**Sero-prevalence**	**Year data collected**	**Total number tested**
Maude	Bangladesh	23.7%	2010	1,209
Richards	Indonesia, Gag Island	9.3%	2003	53
Vallée	Laos, Vientiane	20.7%	2006	2,002
Tay	Malaysia, Western Malaysia	17.9%	2007–2010	280
Spicer	Papua New Guinea	27.9%	2001	140
Premaratna	Sri Lanka	26.3%	2008	57

Ref:Bonell A, Lubell Y, Newton PN, Crump JA, Paris DH. Estimating the burden of scrub typhus: A systematic review. PLoS Negl Trop Dis. 2017 Sep 25;11(9):e0005838. doi: 10.1371/journal.pntd.0005838. PMID: 28945755; PMCID: PMC5634655.

Vector

- Scrub typhus – Trombiculid mite (Larval stage) of *Leptotrombidium spp*
- Larval stage – chiggers (Chiggerosis) – feeding stage on mammals
- Transovarian transmission in vector
- Reservoir - rodents

CDC – Typhus fever/ scrub typhus

Six legged leptotrombiculid larvae

Adult and larval chiggers (mites) on the head of a pin

https://www.cdc.gov/typhus/images/chiggers.jpg

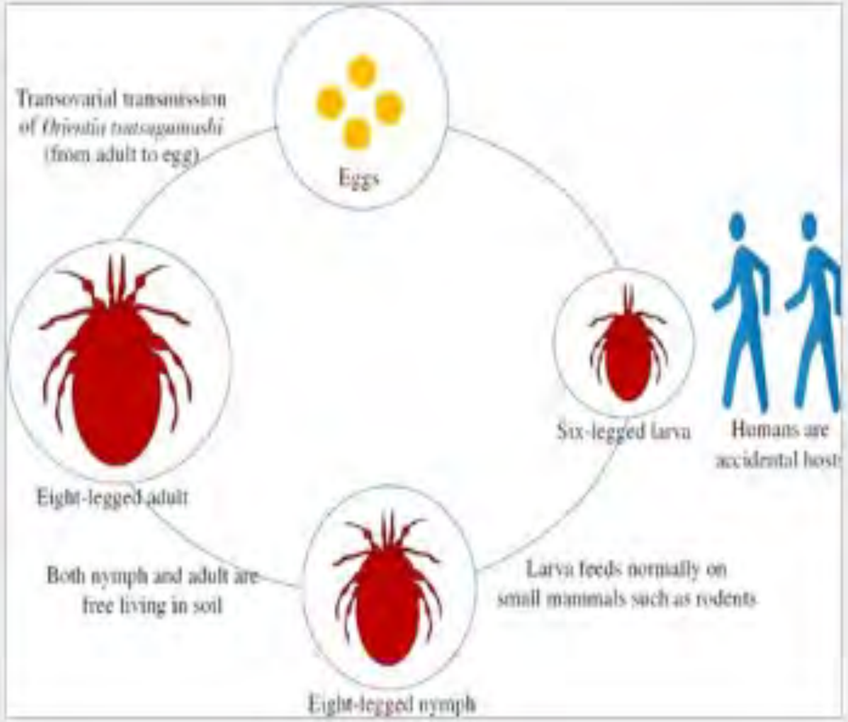


Figure 1: Life cycle of mite *Leptrotrombidium*. The larva (chigger) feeds normally on small mammals but humans are accidental hosts. The *Orientia tsutsugamushi* is transmitted through bite of chigger (larval stage of mite).

- *Leptotrombidium deliense* common vector in India
- Rarely also spread through leech bites – *Rickettsia japonicum*
- Fever occurs on the 4th day after the chigger bite and eschar appears around 7 days

Clinical features – Scrub typhus

- Varies from mild and self limiting to fatal
- Incubation Period: 6 -21 days
- Fever, myalgia, headache, cough, multiple organ involvement
- Delirium, nausea, vomiting, jaundice
- Eschar – site of bite (7 – 80%)
  - Axilla, inguinal, scrotum, inframammary
- Regional lymphadenopathy, hepatomegaly, splenomegaly

Modified from: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's principles of internal medicine, 19e. Mcgraw-hill; 2015.

Case: History and Examination

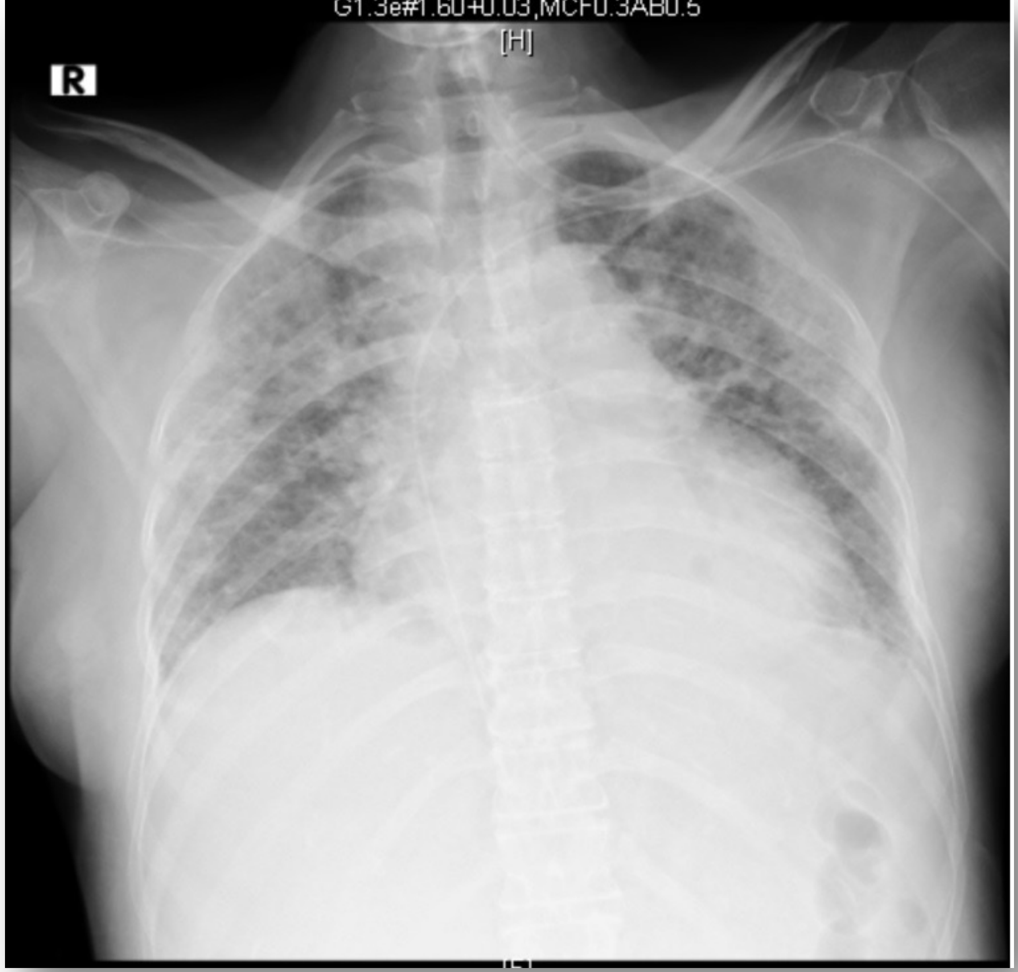
- 72 yr. old teacher from Vellore, retired teacher in South India
- Presents with fever × 10 days and breathlessness × 5 days
- Associated sore throat and myalgia
- Past h/o: Rheumatoid arthritis on steroid (discontinued)
- **On examination**: Vitals normal but pale, scattered wheeze and left groin shows an eschar

Labs

- CBC: TC- 26400/cu.mm (4-11,000/mm^3)
- Platelets – 202,000/ cu.mm, Hb – 10.4 (12-17g%)
- Liver FT and Renal FT: WNL
- NT Pro-BNP – >35,000
- CPK -High
- ECG: Low voltage complexes
- Echo: LV Systolic dysfunction, mild pericardial effusion

➢SARS-CoV-2 : Negative

➢Dengue, Widal, Malaria – negative

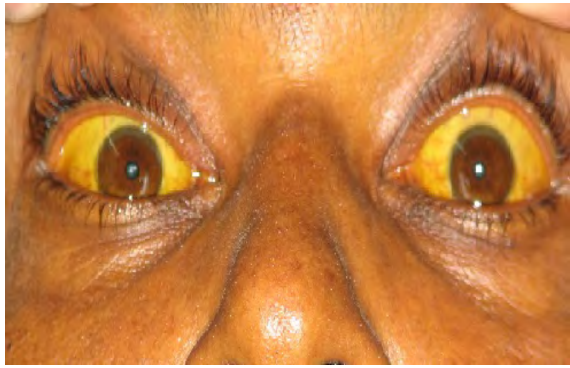


➢Blood culture – No growth

➢**IgM scrub typhus – Negative (1st day of admission) – POSITIVE (3rd day of admission)**

Rickettsial disease: Complications

- ARDS - 44%
- Respiratory involvement (interstitial pneumonitis) in >60%
- Hepatic involvement >80%,
- Pancreatitis
- CVS – Rhythm abnormalities, myocardial involvement with CCF
- Refractory shock – 25%
- Aseptic meningitis or meningoencephalitis– 19%, deafness, cranial nerve palsies, encephalopathy, meningitis, ADEM
- Renal dysfunction – 13%
- MODS – 38%



Varghese GM et al. Int J Infect Dis 2013

Rickettsial disease: Pulmonary manifestations

- 20-70% cases have respiratory symptoms
- Mild bronchitis to severe ARDS
- Dry cough is a common complaint in the initial stage
- CXR:
  - ➢ Initial stages – could be normal
  - ➢ 50-70% show abnormal findings – diffuse reticulo-nodular pattern, ARDS pattern, septal lines and hilar adenopathy

Ref:
1.Wang CC, Liu SF, Liu JW, Chung YH, Su MC, Lin MC. Acute respiratory distress syndrome in scrub typhus. The American journal of tropical medicine and hygiene. 2007 Jun 1;76(6):1148-52.
2.Kim HL, Park HR, Kim CM, Cha YJ, Yun NR, Kim DM. Indicators of severe prognosis of scrub typhus: prognostic factors of scrub typhus severity. BMC infectious diseases. 2019 Dec;19(1):1-5.

ARDS

- 11-20 % incidence
- Higher risk of mortality (22 – 60%)
- Predictors for mortality: Initial presentation of dyspnea, ↓hematocrit, ↑ Total bilirubin, and delayed use of appropriate antibiotics
- Risk factors: Old age, Thrombocytopenia, early pneumonitis
- Indicators for bad outcome: ↓Albumin, ↑ prothrombin time, delay in antibiotic initiation

Ref:Wang CC, Liu SF, Liu JW, Chung YH, Su MC, Lin MC. Acute respiratory distress syndrome in scrub typhus. The American journal of tropical medicine and hygiene. 2007 Jun 1;76(6):1148-52.

1. Clinical
   A. Direct central nervous system involvement
      a. Common
         i. Meningitis
         ii. Meningoencephalitis
         iii. Encephalitis
         iv. Encephalopathy
         v. Seizure
      b. Rare
         i. Stroke
   B. Immune mediated (rare)
      a. Optic neuritis
      b. Myelitis
      c. Acute disseminated encephalomyelitis.
      d. Neuropathy—6th, 7th, mononeuritis multiplex, brachial plexopathy, Guillain-Barre syndrome
2. Investigations
   A. Cerebrospinal fluid
      a. Cells: mild to moderate mononuclear pleocytosis in meningoencephalitis
      b. Protein: mild to moderate increase in meningoencephalitis
   B. CT/MRI: infarction, haemorrhage, subdural haematoma, demyelinating lesion
   C. EEG: generalised theta to delta slowing (common), sharp waves (rare)

CNS manifestations

- Inflammation of endothelium and perivascular tissue – micro-infarctions and ischemia
- Autopsy –
  - ❑Diffuse or focal mononuclear cell infiltration of the leptomeninges
  - ❑Presence of typhus nodules (clusters of microglial cells)
  - ❑Haemorrhage

Meningoencephalitis, Meningitis, encephalitis

GBS, ADEM, Polyneuropathy

Intracranial haemorrhage, stroke

Ref:Misra UK, Kalita J, Mani VE . Neurological manifestations of scrub typhus ,*Journal of Neurology, Neurosurgery & Psychiatry* 2015;86:761-766

Clues towards diagnosis of AUF

Disease	History	Examination	Lab tests
Malaria (*P. falciparum*)	Fever with chills & rigors	Anemia Splenomegaly	Thrombocytopenia ↑ Ind. Bilirubin ±AST, ALT
Dengue	Fever Body ache Anasarca Bleeding	Rash, Petechiae Subconjunctival hemorrhage Hepatomegaly	Leukopenia Thrombocytopenia ↑ Haematocrit
Leptospirosis	Fever Myalgia Headache	Icterus Conj. Suffusion Subconj. h'age	Leukocytosis ↑ Creat, hepatitis, ↑ CPK
Scrub typhus	**Fever, headache** **Breathlessness**	**Eschar**	**Leukocytosis** **Thrombocytopenia** **↑ AST, ALT**
Typhoid	Fever Diarrhea	Coated tongue Splenomegaly	Blood culture Widal

Mortality risk factors - GLOBAL

- Untreated CFR – 6% (0 – 70%) though a decreasing trend noted
- Higher bacterial DNA load – higher risk of mortality
- ***Delay in diagnosis and/or initiation of antibiotic treatment***

Host	• Age, malnutrition, G6PD deficiency, absence of eschar, Higher APACHE II score, elevated creatinine, metabolic acidosis, myocarditis, pneumonitis, delirium, hemorrhage, shock
Pathogen	• Strain of bacteria –invasion, multiplication and dissemination
Vector	• Different species can cause variations in clinical presentation depending on inocula, single or multiple strains

1.Chrispal A, Boorugu H, Gopinath KG, Prakash JA, Chandy S, Abraham OC, Abraham AM, Thomas K. Scrub typhus: an unrecognized threat in South India–clinical profile and predictors of mortality. Tropical Doctor. 2010 Jul;40(3):129-33.
2.Taylor AJ, Paris DH, Newton PN. A systematic review of mortality from untreated scrub typhus (Orientia tsutsugamushi). PLoS Negl Trop Dis. 2015 Aug 14;9(8):e0003971.

Mortality risk factors in South East Asia

Risk Factors Leading to Fatal Outcome in Scrub Typhus Patients

Chang-Seop Lee, Jeong-Hwan Hwang, Heung-Bum Lee, and Keun-Sang Kwon*
Departments of Internal Medicine, Preventive Medicine, Chonbuk National University Medical School, and Research Institute of Clinical Medicine, Jeonju, Republic of Korea

- 297 patients with scrub typhus were included in the study
- Mortality rate : 6.1%
- Multivariate logistic regression analysis revealed **absence of eschar, event of intensive care unit admission and higher APACHE II score** were independent predictive variables.

Ref:Lee CS, Hwang JH, Lee HB, Kwon KS. Risk factors leading to fatal outcome in scrub typhus patients. Am J Trop Med Hyg. 2009 Sep;81(3):484-8. PMID: 19706919.

Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome

George M. Varghese [a,*], Jeshina Janardhanan [a], Paul Trowbridge [b], John V. Peter [c], John A.J. Prakash [d], Sowmya Sathyendra [e], Kurien Thomas [a], Thambu S. David [e], M.L. Kavitha [f], Ooriapadickal C. Abraham [a], Dilip Mathai [a]

- 154 patients evaluated with fever and non-specific symptoms.
- Factors associated with mortality included jaundice ($p = 0.02$), hypotension requiring vasoactive agents ($p = 0.001$), ARDS ($p = 0.02$), need for mechanical ventilation ($p = 0.004$), and renal failure S.creatinine >2.5 mg/dl ($p = 0.006$).
- The duration of symptoms and duration of ventilation tended to be higher in non-survivors
- The phylogeny showed 17 (65%) clustering with the Kato-like group and eight (31%) with the Karp-like group

Ref:Varghese GM et.al. Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome. Int J Infect Dis. 2013 Nov;17(11):e981-7. doi: 10.1016/j.ijid.2013.05.017. Epub 2013 Jul 26. PMID: 23891643.

Diagnosis

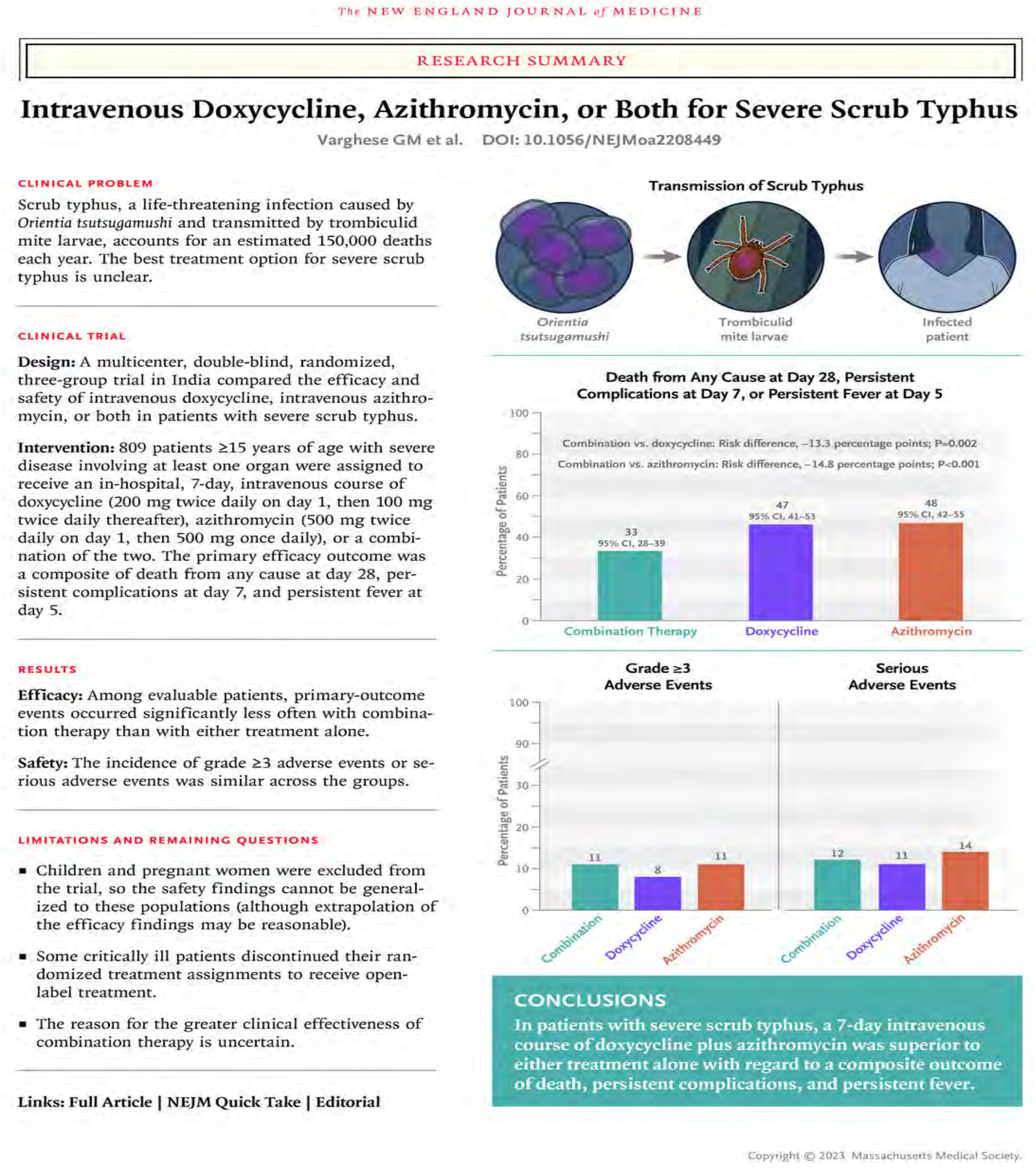
<u>GOLD STANDARD TESTS</u>: Various Ag – Karp, Kato or Gilliam

- ***<u>Immunofluorescence assay (IFA)</u>***: Costly and requires technical expertise
  - Sensitivity 70% and specificity of 95%
- ***<u>Indirect immunoperoxidase assay (IPA):</u>*** Does not require a fluorescent microscope

- ***<u>Weil-Felix:</u>*** It demonstrates agglutinins to *Proteus vulgaris* strain OX19, OX2 and *Proteus mirabilis* OXK after 5-7 days of fever onset
  - ➢ Lacks sensitivity and specificity
- ***<u>IgM and IgG ELISA</u>***: immunoglobulin M (IgM) capture assays, sensitive, significant IgM titre is observed at the end of 1st week
- ***<u>Polymerase chain reaction (PCR):</u>*** whole blood/buffy coat fraction or tissue specimen, 56 kDa and/or 47 kDa surface antigens amplified, specificity approaches 100% (95 – 100%) in the 1st week

Antibiotic Management

Drug	Dose	Contraindication/ ADR
Doxycycline (DOC)	**100mg BD for 7 days or 3 afebrile days** **Children: 4.4mg/mg/kg/day in 2 divided doses**	**Pregnancy, Young children** **ADR: Photosensitivity, GI disturbances**
Rifampin	600-900 mg/day for 7 days	
Azithromycin (Useful in pregnant adults)	500 mg for 7 days	
Chloramphenicol	500 mg every 6 hours for 7 days	**Pregnancy and children** **Aplasia**


The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Intravenous Doxycycline, Azithromycin, or Both for Severe Scrub Typhus

Varghese GM et al. DOI: 10.1056/NEJMoa2208449

CLINICAL PROBLEM

Scrub typhus, a life-threatening infection caused by *Orientia tsutsugamushi* and transmitted by trombiculid mite larvae, accounts for an estimated 150,000 deaths each year. The best treatment option for severe scrub typhus is unclear.

CLINICAL TRIAL

Design: A multicenter, double-blind, randomized, three-group trial in India compared the efficacy and safety of intravenous doxycycline, intravenous azithromycin, or both in patients with severe scrub typhus.

Intervention: 809 patients ≥15 years of age with severe disease involving at least one organ were assigned to receive an in-hospital, 7-day, intravenous course of doxycycline (200 mg twice daily on day 1, then 100 mg twice daily thereafter), azithromycin (500 mg twice daily on day 1, then 500 mg once daily), or a combination of the two. The primary efficacy outcome was a composite of death from any cause at day 28, persistent complications at day 7, and persistent fever at day 5.

RESULTS

Efficacy: Among evaluable patients, primary-outcome events occurred significantly less often with combination therapy than with either treatment alone.

Safety: The incidence of grade ≥3 adverse events or serious adverse events was similar across the groups.

LIMITATIONS AND REMAINING QUESTIONS

- Children and pregnant women were excluded from the trial, so the safety findings cannot be generalized to these populations (although extrapolation of the efficacy findings may be reasonable).
- Some critically ill patients discontinued their randomized treatment assignments to receive open-label treatment.
- The reason for the greater clinical effectiveness of combination therapy is uncertain.

Links: Full Article | NEJM Quick Take | Editorial

CONCLUSIONS

In patients with severe scrub typhus, a 7-day intravenous course of doxycycline plus azithromycin was superior to either treatment alone with regard to a composite outcome of death, persistent complications, and persistent fever.

Among 794 patients with severe scrub typhus, mortality with combination was 33%, doxycycline alone 47% and Azithromycin alone 48%

- Doxycycline 200mg BD x 1 day f/b 100mg BID for 6 days
- Azithromycin 500mg BID x day 1 f/b 500mg OD for 6 days

GM Varghese et al. N Engl J Med 2023;388:792-803.

The NEW ENGLAND JOURNAL of MEDICINE

Case

- 38 year old gentleman an Indian citizen visited Ethiopia 12 days prior to present OP visit
- He visited there for some official business reason and was put up in a place close to the forest – eco lodge
- He presented with high grade fever and severe headache of 8 days duration

- With thanks to

Dr Sanket Mankad

History contd…….

- He denied a rash, jaundice, vomiting
- Mild nausea
- He was not on malaria prophylaxis as he from India and assumed he did not need it
- It was a short business trip of 5 days but he took walks in the forest
- He loved the local cuisine and indulged himself but in the hotel itself
- He took the yellow fever vaccine on advice of his local doctor
- He did not take typhoid and hepatitis A vaccines

On examination

- General exam was normal
- Vitals were stable except that he was febrile
- Systemic exam was normal

Which is the likely causative pathogen?

1. *Rickettsia africae*
2. *Brucella melitensis*
3. *Bacillus anthracis*
4. *Francisella tularensis*
5. *Orientia tsutsugamushi*

- 2% are due to rickettsioses
- 20% of above end up hospitalized
- 2nd most common cause in Africa of a systemic febrile illness
- Treat while awaiting confirmation with tetracyclines

Treatment is Doxycycline and they magically recover

Prevention

- Maintenance of body hygiene to prevent louse infestation
- Visual inspection of clothing to ensure there are no ticks, light coloured clothing with long sleeves and trousers
- Insecticides: Can be used to control ticks, mites, mosquitoes, fleas
- Insect repellents: DEET >10% but <50%, Picaridin, Oil of lemon eucalyptus
- Insectcide treated clothes apply 24-48 hours before travel <0.5% Permethrin
- No vaccines available
- Prophylaxis: If Doxycycline for malaria can protect against rickettsia and Leptospirosis too

– so in high risk travellers for short term use but not routinely recommended

Summary of Rickettsial disease

- Scrub typhus is a re-emerging cause of acute febrile illness in South and South East Asia, Middle east and even in South America
- Good epidemiological history and a pathognomonic eschar is almost confirmatory of diagnosis
- Mortality varies from 6-24% and predictors are prolonged duration of fever, absence of eschar and a high APACHE II score
- Serological tests help with early diagnosis in all rickettsia
- Doxycycline drug of choice for all rickettsia
- Antibiotic options are limited and increased fever defervescence and delayed clinical response is being noted