Rickettsial Diseases

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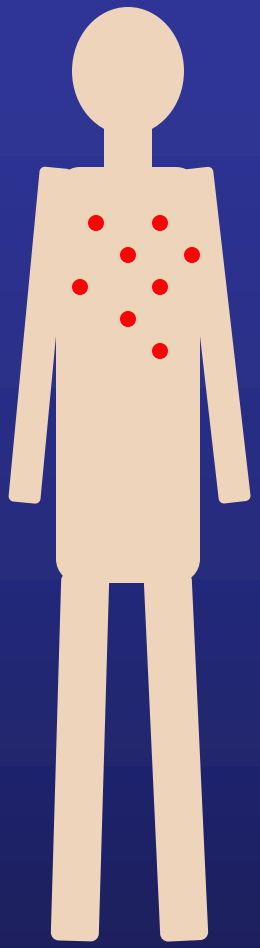
Outline

- Introduction
- Common clinical features
- Spotted fever group rickettsioses
- Typhus group rickettsioses
- Scrub typhus
- Ehrlichiosis and anaplasmosis
- Diagnosis
- Treatment

Vectors of Transmission

Ticks

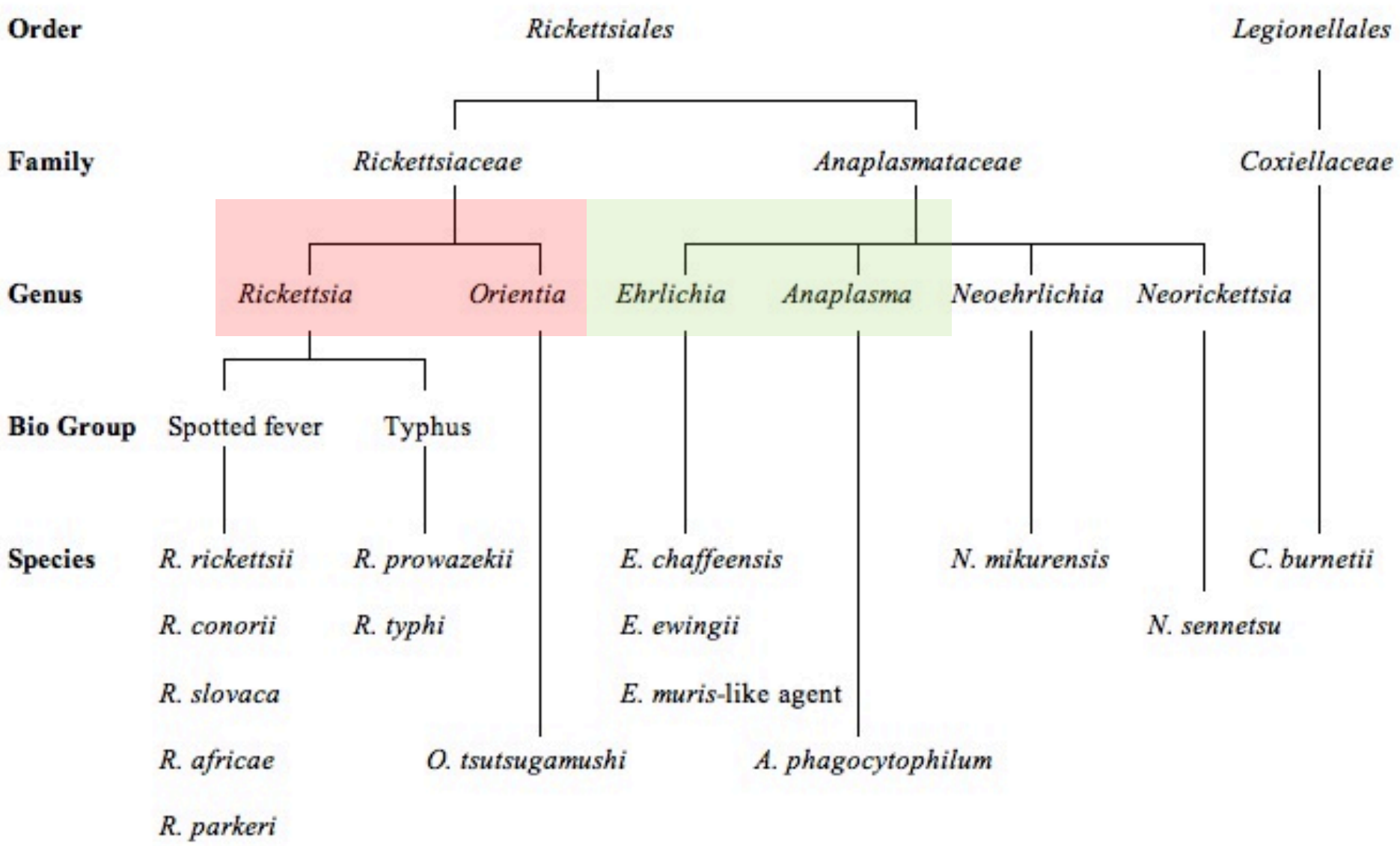
Lice



Fleas

Mites

Taxonomy of representative human pathogens in the order *Rickettsiales*



Obligately Intracellular Organisms

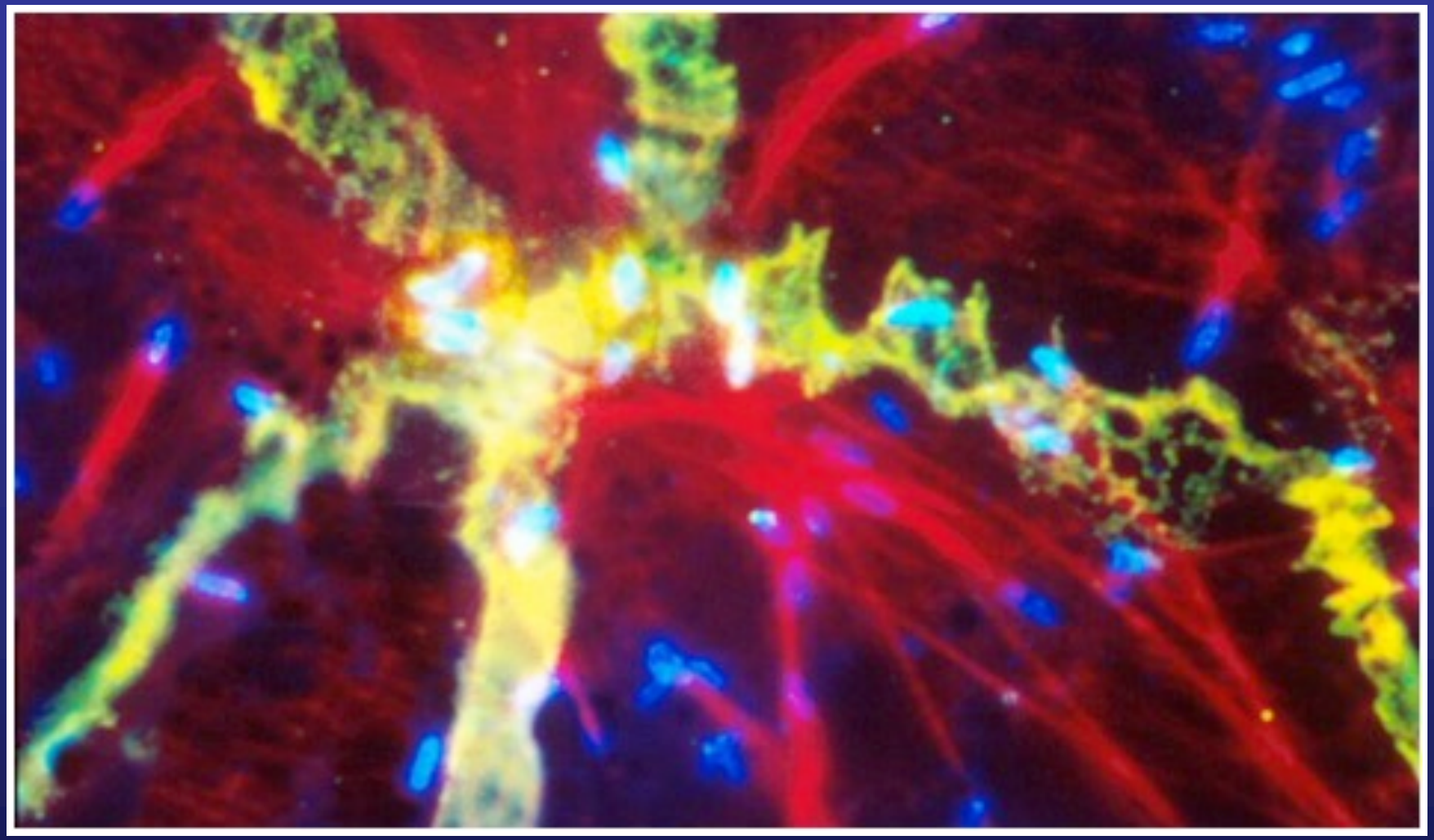
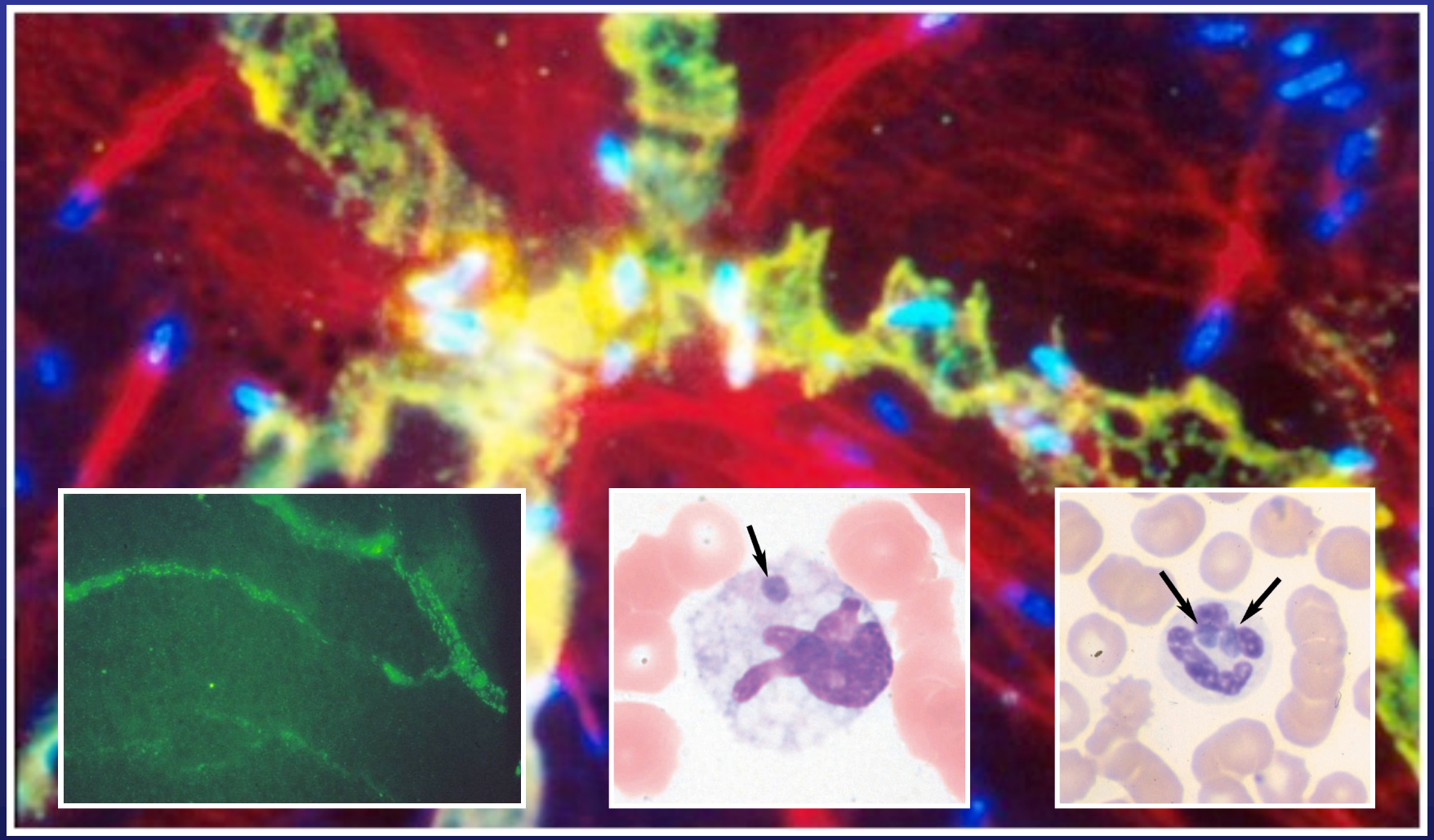


Photo courtesy of David Walker

Obligately Intracellular Organisms



Rickettsia and *Orientia*
= Endothelial cells

Ehrlichia chaffeensis
= Monocytes

Anaplasma
= Neutrophils

Endothelial Infection

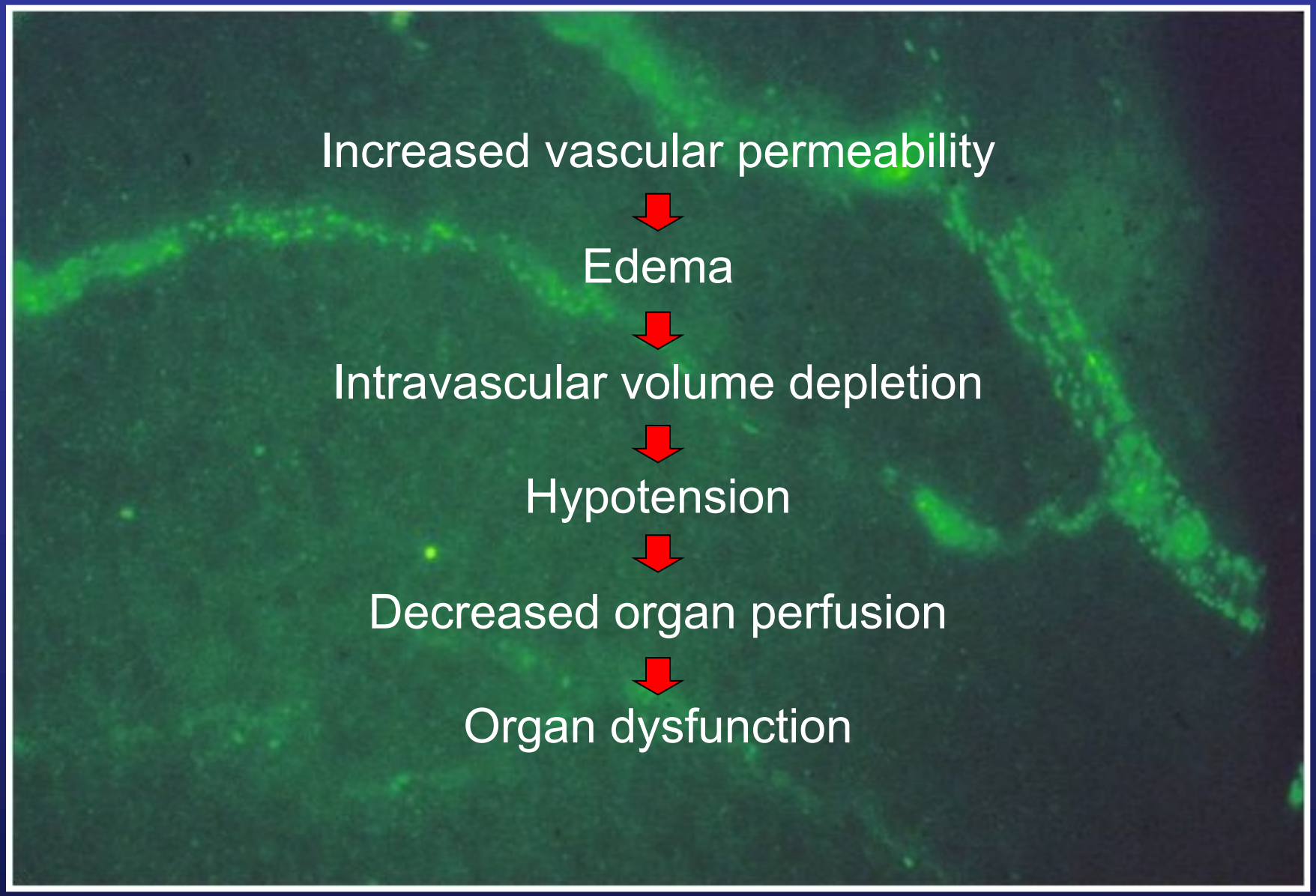


Photo courtesy of David Walker

Overlapping Clinical Features

Overlapping Clinical Features

- All are undifferentiated febrile illnesses with a flu-like quality
- Usually of sudden onset
- Universal or frequent manifestations include:
  - Fever
  - Headache
  - Myalgias
  - Malaise

Overlapping Clinical Features

	Frequency		
	~ 50%	~ 30%	< 15%
GI	Nausea/Vomiting	Abdominal pain	Diarrhea
Pulmonary		Cough	Respiratory failure
Renal			Acute Kidney Injury
Neurologic			Meningoencephalitis Confusion Stupor Coma

Overlapping Clinical Features

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	~ 50%	~ 30%	< 15%
GI	Nausea/Vomiting	Abdominal pain	Diarrhea
Pulmonary		Cough	Respiratory failure
Renal			Acute Kidney Injury
Neurologic			Meningoencephalitis Confusion Stupor Coma

More Pathogenic Organism

Less Pathogenic Organism

Overlapping Laboratory Features

	Rickettsioses	Scrub typhus	Ehrlichiosis & Anaplasmosis
↑ LFT	++	+++	+++
↓ Platelets	++	++	+++
↓ WBC	+	+	++
↑ WBC	+	+	-
↓ Hbg	+	+	++
↓ Na^+	++	-	-

+++ Very frequent (≥ 80%)

++ Frequent (40 – 80%)

+ Occasional (≤ 40%)

- Not a feature

Spotted Fever Group Rickettsioses

Epidemiology of Spotted Fever Group Rickettsiosis

Organism	Disease	Severity	Distribution
R. rickettsii	Rocky Mountain spotted fever	++++	Americans
R. conorii	Mediterranean spotted fever	+++	Mediterranean basin Africa, Asia
R. africae	African tick bite fever	++	Sub-Saharan Africa
R. parkeri	Maculatum disease	++	Americas
R. slovaca	Tick-borne lymphadenopathy	+	Europe
R. sibirica	North Asian tick typhus	++	Eurasia, Africa
R. honei	Flinders Island spotted fever	++	Southern Australia, Thailand
R. japonica	Japanese spotted fever	++	Japan, China
R. heilongjiangensis	Far Eastern spotted fever	++	Eastern Asia
R. aeschlimannii	Not named	+	Southern Europe, Africa
R. massiliae	Not named	+	South America, Europe
R. monacensis	Not named	+	Europe
Rickettsia 364D	Not named	+	California

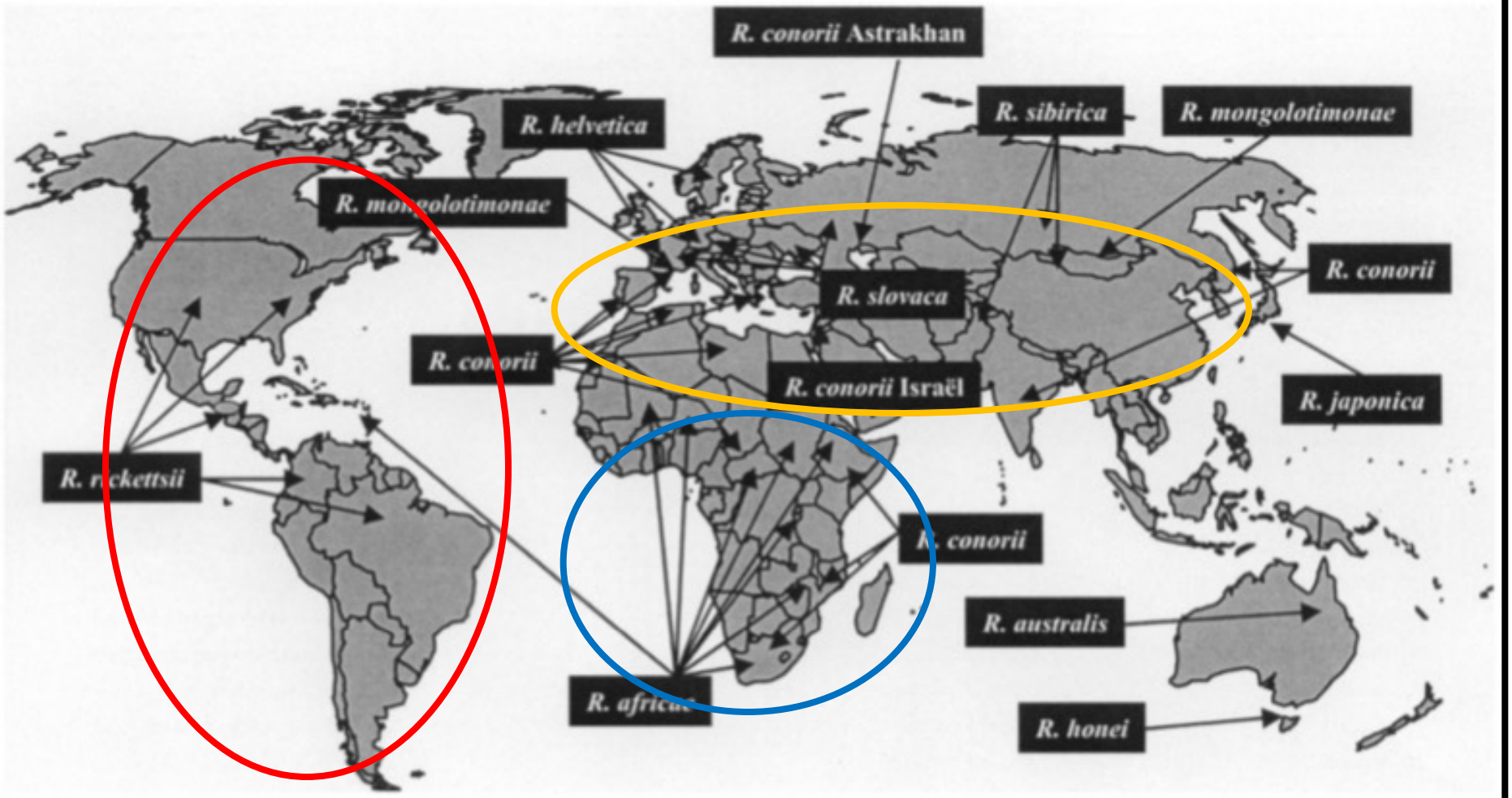


Figure 11. Geographic distribution of tickborne pathogenic rickettsiae

R. rickettsii = Rocky Mountain spotted fever, Brazilian spotted fever

R. conorii = Mediterranean spotted fever, Boutonneuse fever, Israeli spotted fever, Indian tick typhus

R. africae = African tick bite fever

Rickettsia rickettsii - Rocky Mountain Spotted Fever

- United States
- Mexico
- Costa Rica
- Panama
- Columbia
- Brazil
- Argentina

Vectors of *Rickettsia rickettsii*

Dermacentor variabilis

Dermacentor andersoni

Amblyomma cajennense

Rhipicephalus sanguineus

RMSF - Clinical Features

- Sudden Onset of:
  - Fever - 99 - 100%
  - Myalgias 73 - 80%
  - Headache 79 - 91%
- Rash
  - Occurs in ~ 90%
    - Day 1 in ~ 15%
    - Day 1 - 3 in ~ 50%
    - Day 5 - 6 in ~ 20%

GI Manifestations

• Nausea and/or vomiting	38 - 56%
• Abdominal pain	30 - 34%
• Diarrhea	9 - 20%
• Jaundice	8 - 9%

Neurologic Manifestations

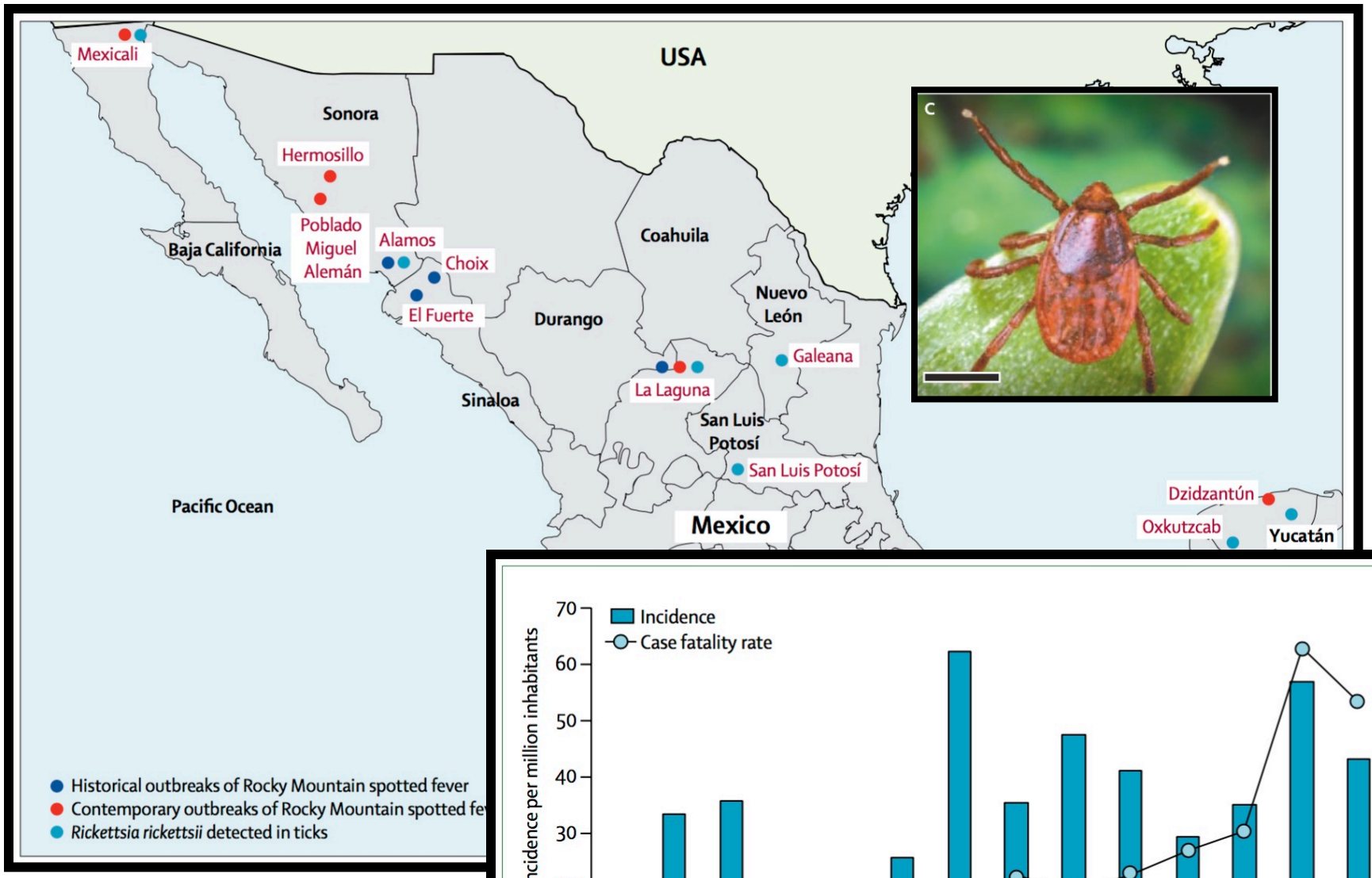
• Confusion	28%
• Stupor or delirium	21 - 26%
• Ataxia	5 - 18%
• Coma	9 - 10%
• Seizures	8%
• CSF	
– Pleocytosis	34 - 38%
– Elevated protein	30 - 35%

Rash of Rocky Mountain Spotted Fever

- Rash occurs in > 90% (only 50% in first 3 days of illness)
- Rash starts on wrists & ankles then progresses to trunk
- Rash on palms & soles (36 - 82%); after day 5 in 43%
- No inoculation eschar

Important Characteristics of RMSF

- Usually sporadic in most of U.S.; can occur in clusters in Mexico, Arizona, Brazil
- Usually very few ticks infected (*R. rickettsii* detrimental to tick life cycle)
- Damage to microcirculation -> hypovolemia -> gangrenous skin or digits (4%)
- Case fatality in U.S. (23% untreated; 4% treated)
- Case fatality upwards of 50% in Brazil and Mexico



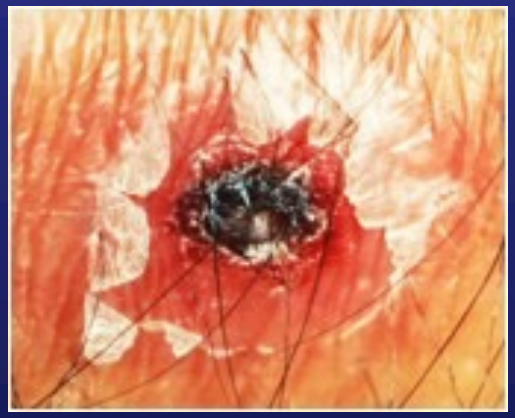
Alvarez-Hernandez. RMSF in Mexico. Lancet Inf Dis. 2017; e189-e186.

Figure 11. Geographic distribution of tickborne pathogenic rickettsiae

R. conorii = Mediterranean spotted fever, Boutonneuse fever, Kenya tick typhus, Israeli spotted fever, Indian tick typhus, Astrakhan spotted fever

Rickettsia conorii - Mediterranean Spotted Fever

Rhipicephalus sanguineus
(Brown dog tick)



Eschar at site of tick bite

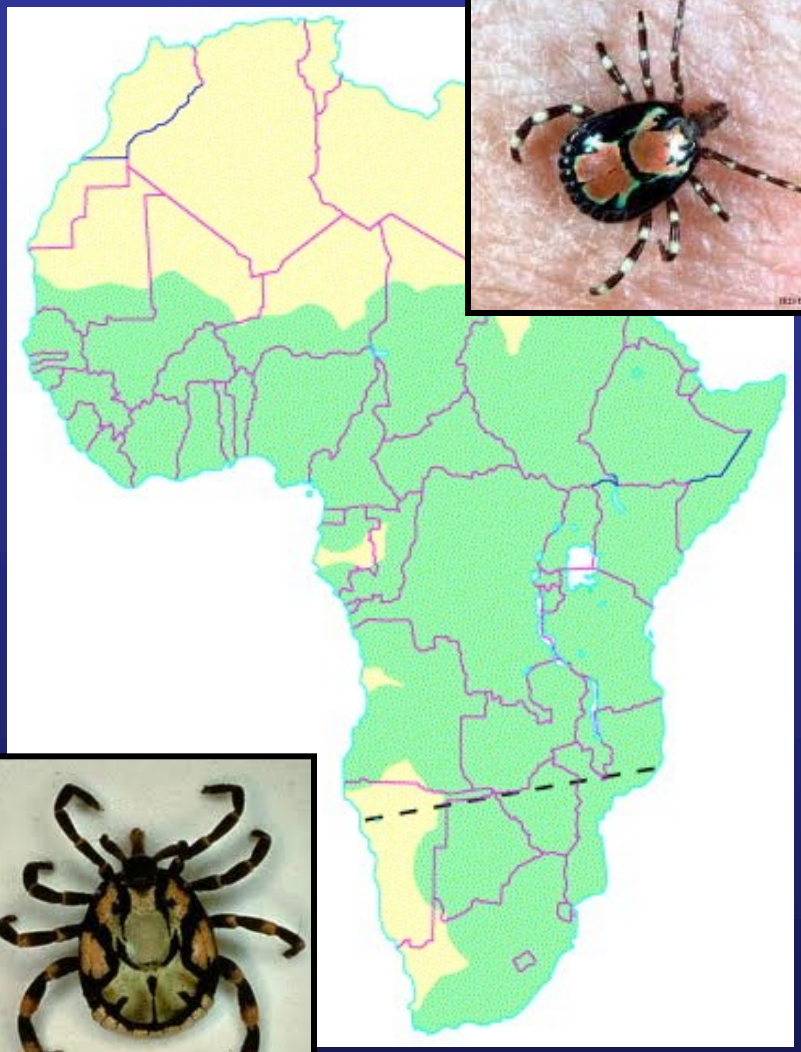
- Caused by the bite of the brown dog tick

- Fever - 100%
- Myalgias 73 - 80%
- Headache 56%
- Rash 97%
- Eschar 72%

- Increased AST 35%
- Thrombocytopenia 25%
- Hyponatremia 25%
- Azotemia 6%

- Untreated case fatality ~2%

Rickettsia africae - African Tick Bite Fever



- Infection in those traveling to sub-Saharan Africa
- Most common SFG infection in travelers
- *Amblyomma* ticks are aggressive feeders
- Ticks frequently infected

Rickettsia africae - African Tick Bite Fever

Eschar in a woman who removed several attached ticks while visiting Kruger National Park in South Africa.

- Eschar occurs in 95%
- Multiple eschars in 54%
- Adenopathy in 50%
- Macular rash in 50%
- No deaths reported in literature

Pathogenicity of Rickettsiae

African Tick Bite Fever

Rickettsia africae

Least Pathogenic

No deaths reported in literature

Eschar

Mediterranean spotted fever

Rickettsia conorii

Untreated fatality ~2%

Eschar

RMSF

Rickettsia rickettsii

Most Pathogenic

Case fatality ~ 4%
Untreated fatality 23%

No eschar

Typhus Group Rickettsioses

The Confusing Diseases Called Typhus

Greek word “tuphos” = smoke (refers to cloudy sensorium)

- *Rickettsia prowazekii*
  - Typhus
  - Epidemic typhus
  - Louse-borne typhus
  - Louse-borne epidemic typhus
  - Sylvatic typhus
  - Flying squirrel associated typhus
  - Brill-Zinsser Disease
  - Recrudescent typhus
  - Jail fever
  - Exanthematic typhus
- *Rickettsia typhi*
  - Murine typhus
  - Endemic typhus
  - Flea-borne typhus
  - Shop typhus
  - Mexican typhus or “Tarbadillo”
  - 21-day fever
- *Orientia tsutsugamushi*
  - Scrub typhus

Rickettsia prowazekii – Typhus (Epidemic Typhus; Louse-Borne Typhus)

- Disease of war, famine, natural disaster, unsanitary conditions
- Usually during cold months
- Presence of macular rash is variable (starts on trunk and spreads centrally)
- Untreated mortality 50-60%; treated mortality ~4%.

Transmitted by the body louse (*Pediculus humanus humanus*)

- Recent outbreaks: Burundi, Rwanda, Congo, Algeria, Russia, Peru, France, Ethiopia

Typhus - Clinical Features

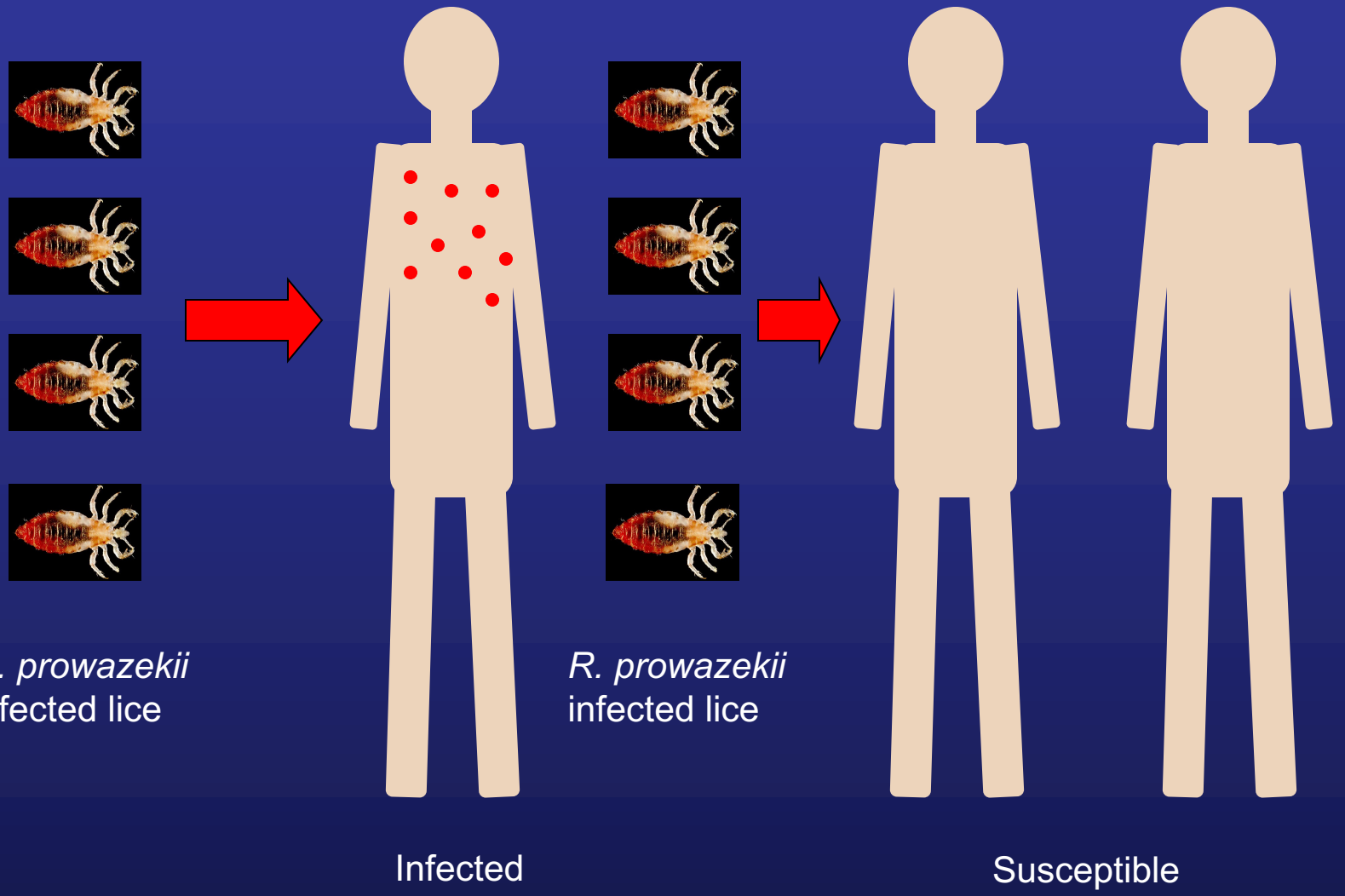
Symptoms	
Fever	100%
Headache	100%
Rash	38%
Myalgias	100%
Nausea/Vomiting	57%
Cough	70%

Laboratory Features	
Thrombocytopenia	43%
Transaminitis	63%
Hypoproteinemia	38%

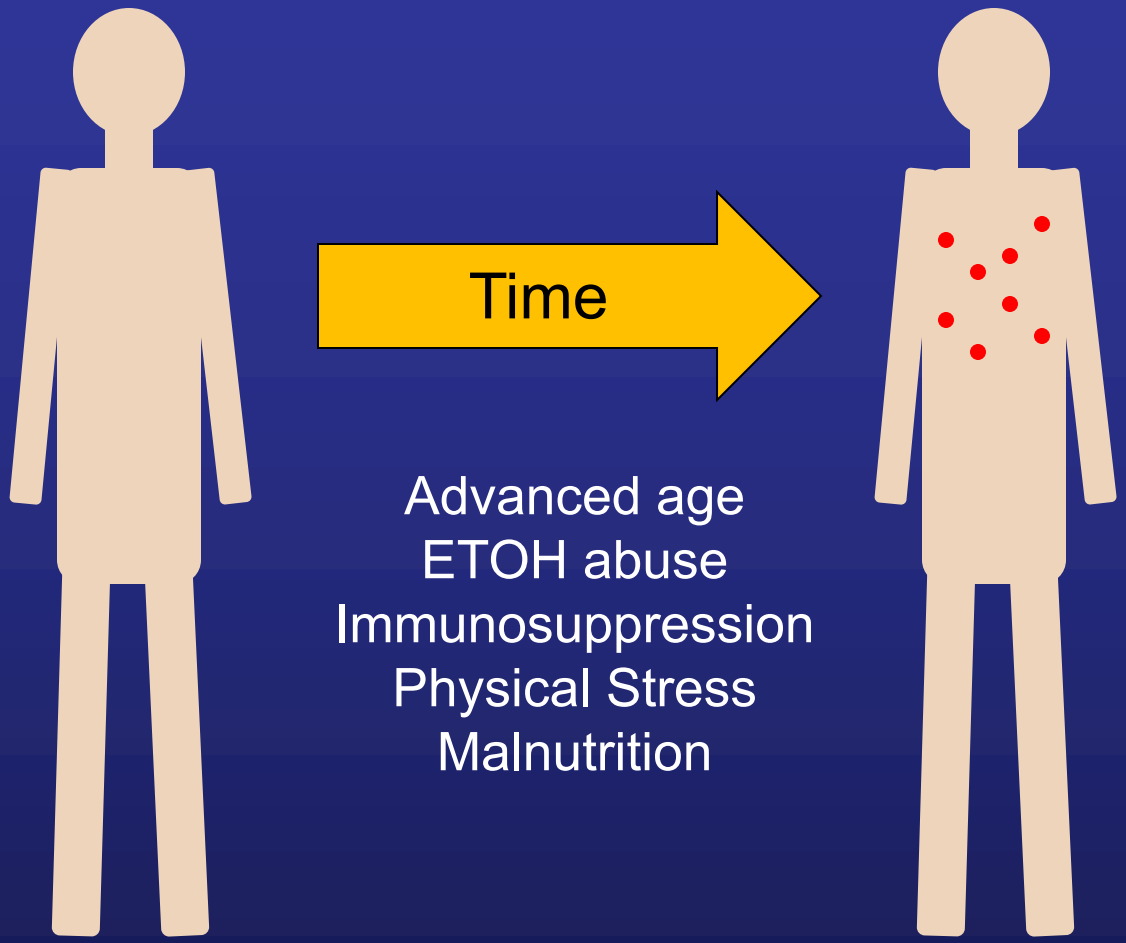
Fournier PE, et al. Human pathogens in body and head lice. Emerg Infect Dis. 2002; 8:1515-1518

Perine PL, et al. A clinico-epidemiological study of epidemic typhus in Africa. Clin Infect Dis. 1992; 14:1149-1158.

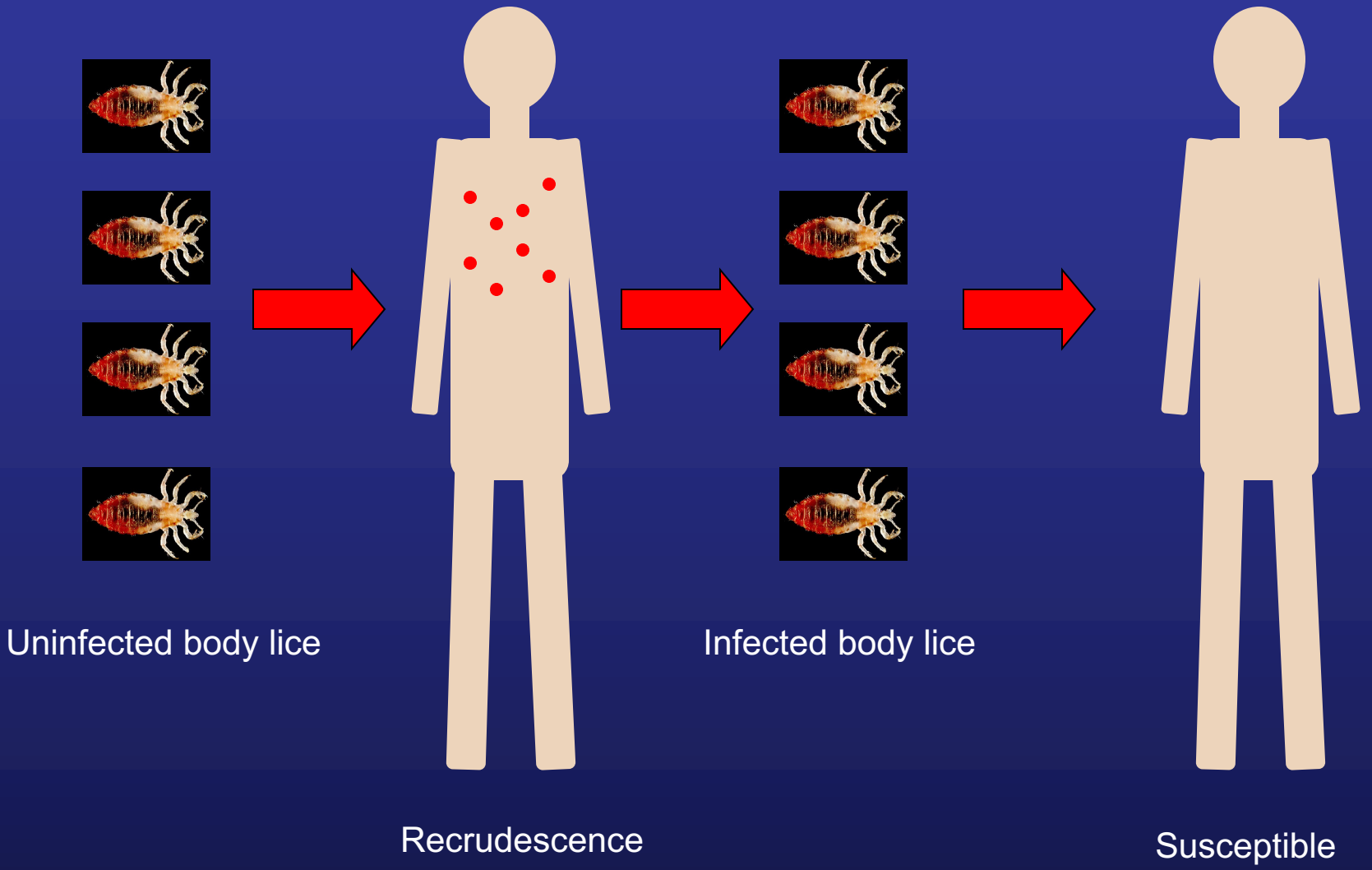
Typhus - Transmission



Recrudescent Typhus (Brill-Zinsser Disease)



Typhus - Recrudescence



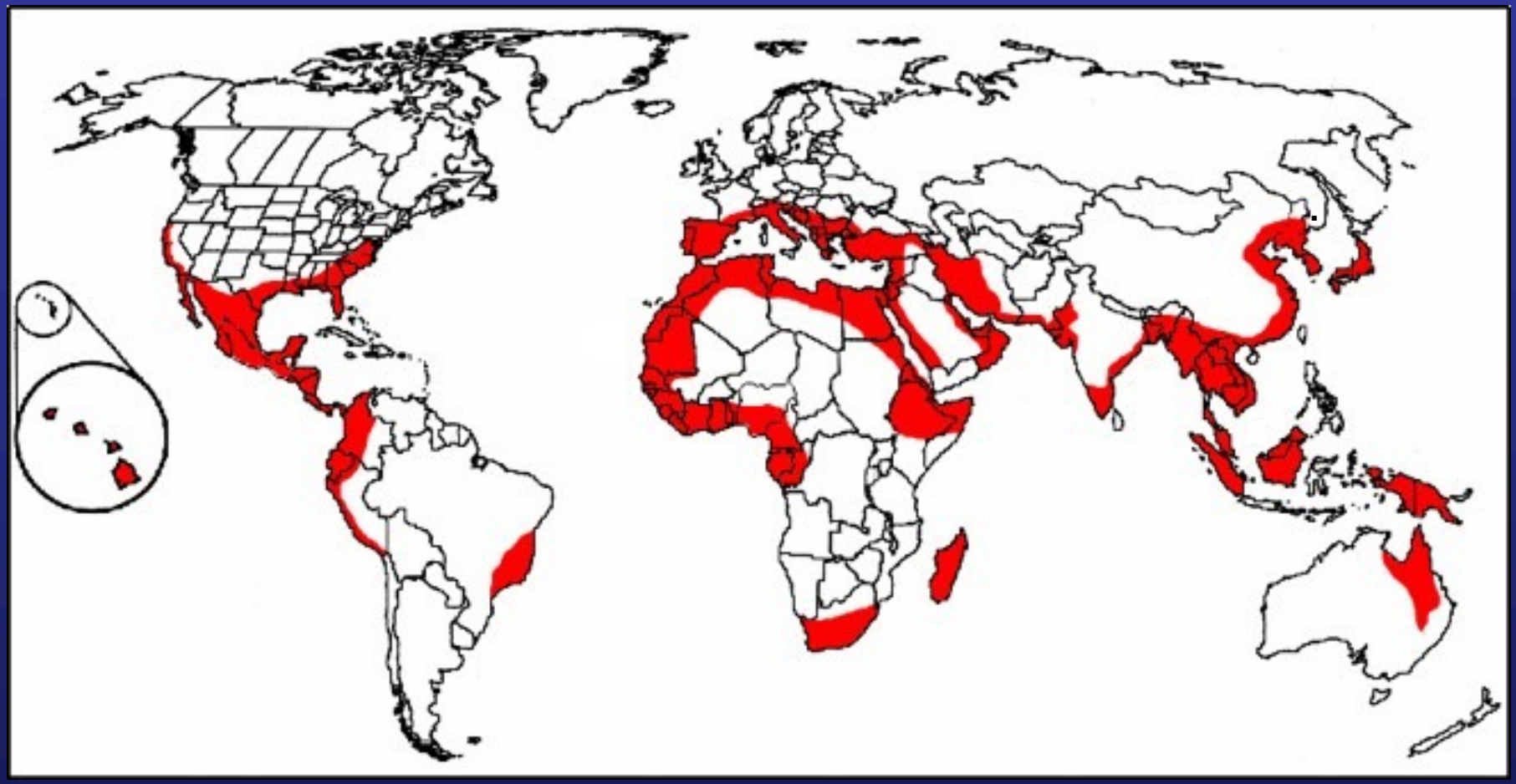
Sylvatic typhus (Flying squirrel associated typhus)

- *R. prowazekii* has been isolated from *Glaucomys volans*
- Contact with flying squirrels has led to sporadic cases in the United States
- Flying squirrel associated typhus appears to be milder than louse-borne typhus
- Clusters of cases have been described

Glaucomys volans

Sonenshine DE, et al. Epizootiology of epidemic typhus (*Rickettsia prowazekii*) in flying squirrels. Am J Trop Med Hyg. 1978;27:339-349.

Rickettsia typhi – Murine Typhus (Endemic Typhus; Flea-Borne Typhus)



Geographic distribution of Murine Typhus

Murine Typhus - Clinical Features

Symptoms:

- Fever 98%
- Headache 75%
- Chills 66%
- Rash 54%
- Myalgias 46%
- Malaise 29%
- Nausea 48%
- Vomiting 40%

History of flea bites 26%

Rodent exposure 29%

Rash

- Macular 49%
- Maculopapular 29%
- Located on trunk 88%

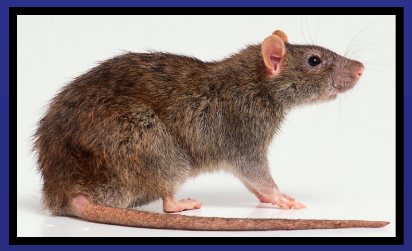
Laboratory Features

- Leukopenia ~50%
- Thrombocytopenia ~50%
- Transaminitis ~70%
- Hypoproteinemia ~45%
- Hypoalbuminemia ~90%
- Hyponatremia ~60%

Case Fatality < 1%

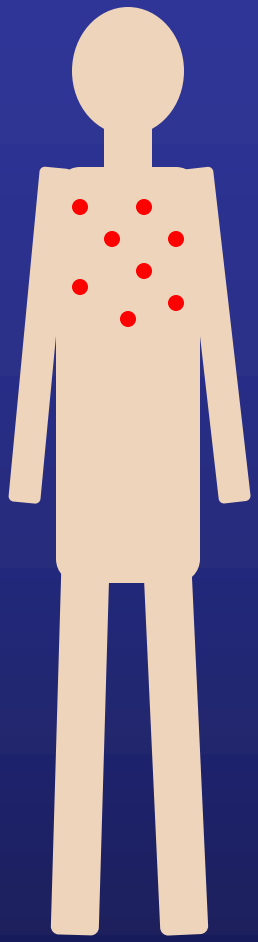
R. typhi - Transmission

Urban cycle



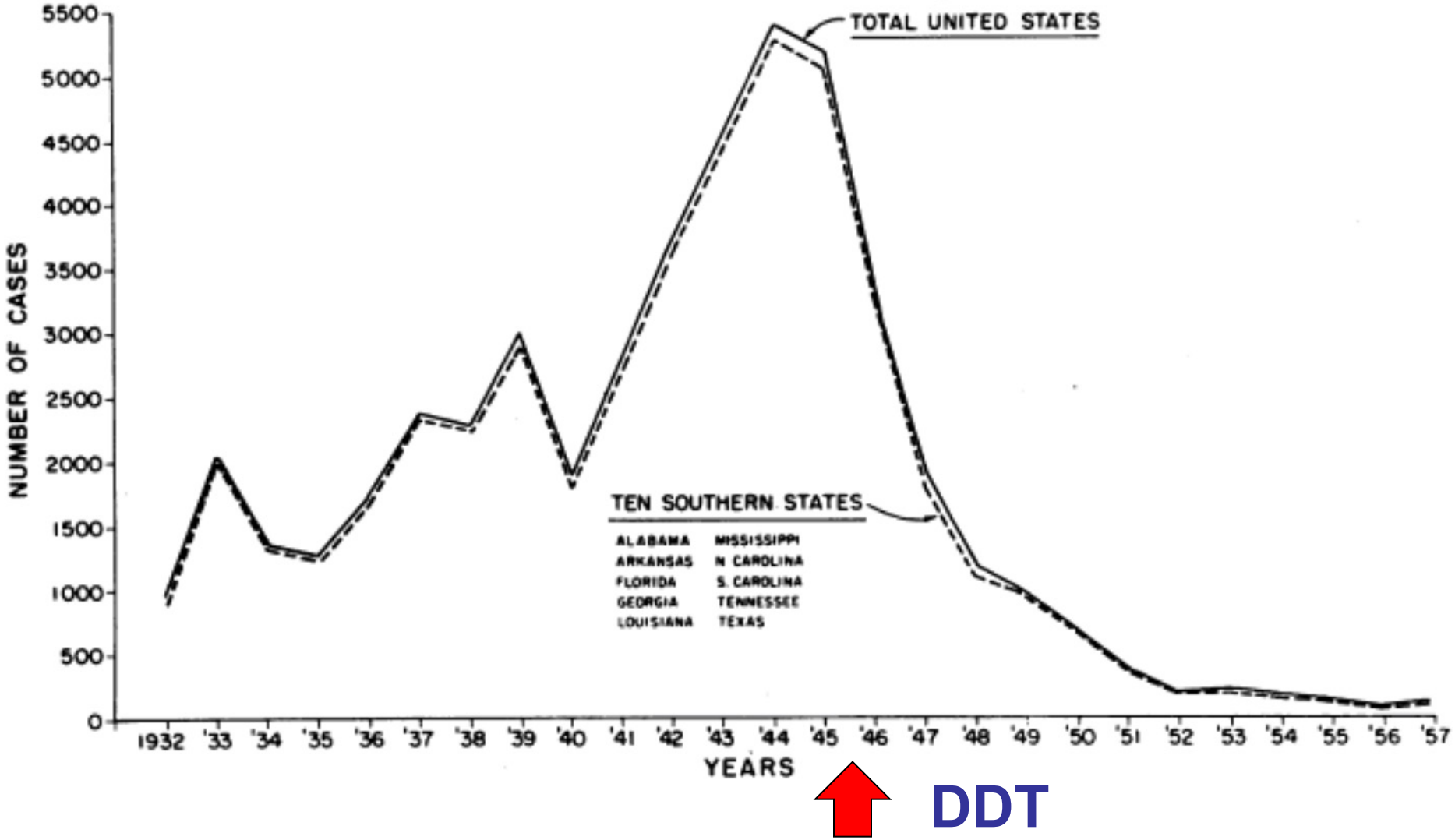
Rattus sp.

Xenopsylla cheopis
(Oriental rat flea)



Azad AF, et al. Flea-borne rickettsioses: Ecologic considerations. EID. 1997; 3:319-327.

Figure 1. Annual total of reported murine typhus fever cases in the United States, 1932–57



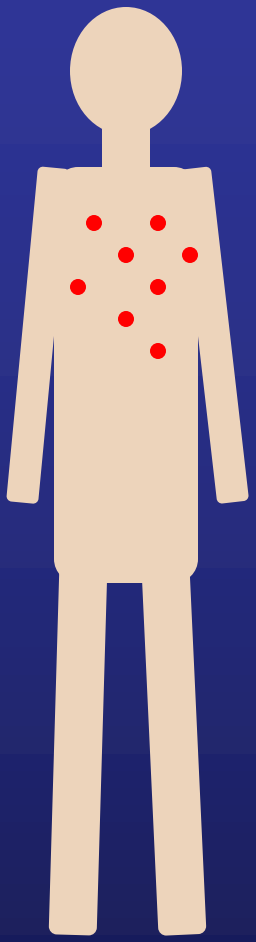
Love et al. Murine typhus investigations in southwestern Georgia. Pub Health Rep. 1960;75:429-440.

R. typhi - Transmission

Suburban cycle

Didelphis
(Opossum)

Ctenocephalides felis
(Cat flea)



Azad AF, et al. Flea-borne rickettsioses: Ecologic considerations. EID. 1997; 3:319-327.

Rickettsia typhi – Murine typhus

- Rash is macular and may be very faint
- Rash occurs in ~ 50%
- Flea bites or fleas in environment are often unnoticed
- Case fatality is ~ 0.4%

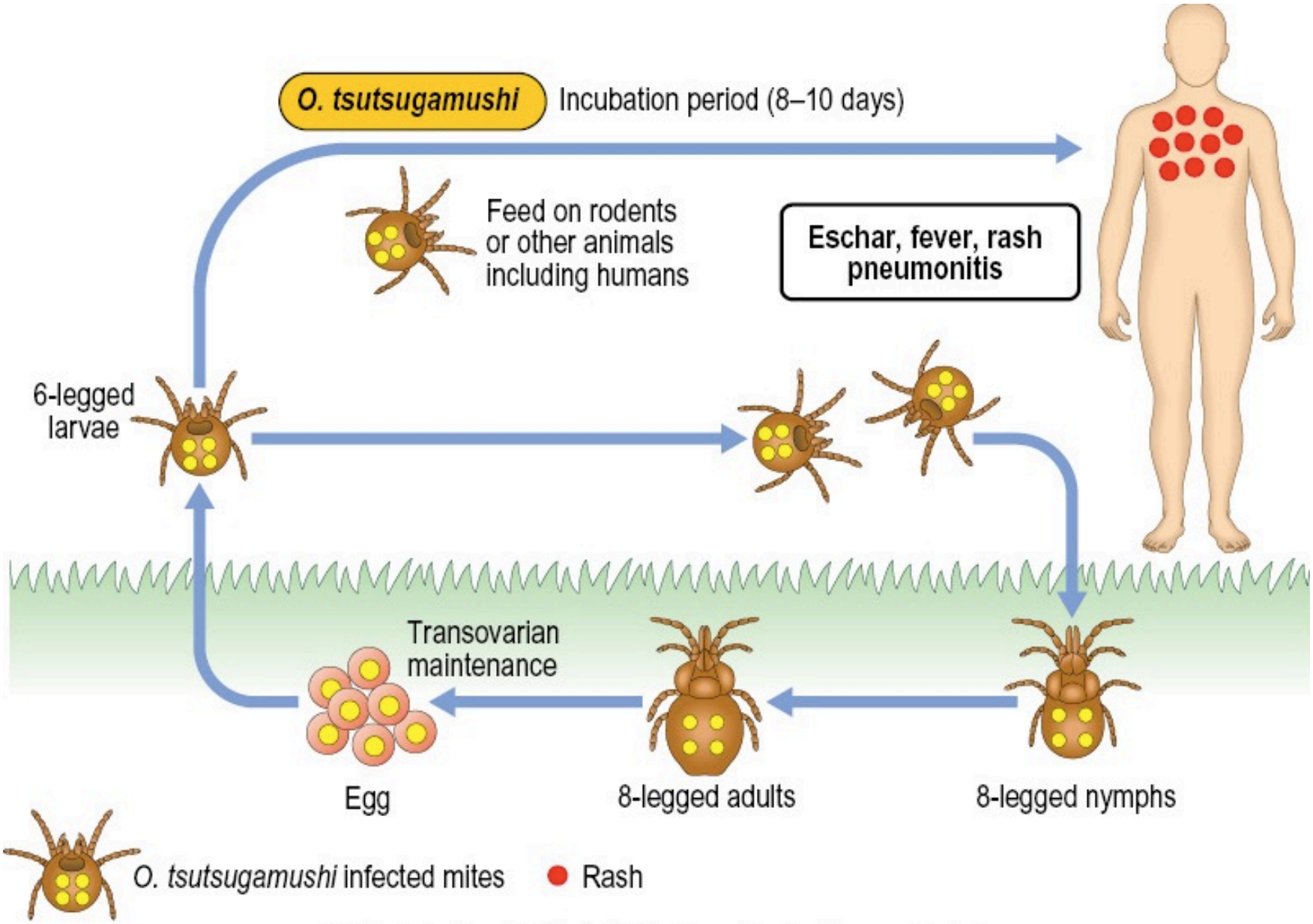
Scrub Typhus

Scrub Typhus – *Orientia*

- Reclassified from rickettsiae to separate genus in 1995
- Three species:
  - *Orientia tsutsugamushi*
  - *Orientia chuto*
  - *Candidatus* Orientia chiloensis
- Numerous *O. tsutsugamushi* strains
  - Karp, Kato, Gilliam (and many more)
  - Tremendous antigenic variation

Classic Scrub Typhus (*O. tsutsugamushi*) Distribution

Orientia tsutsugamushi is transmitted by the larval chigger



Scrub Typhus - Epidemiology

- Transmission occurs during the seasonal activity of the chigger.
  - During warmer months in more temperate regions
  - Year-round in more tropical regions
- Disease transmission occurs in rural, village, and suburban areas.
- Inhabitants of city centers are not at risk.

Scrub Typhus - Signs & Symptoms

- Illness begins suddenly after ~ 10 days of incubation

• Fever	100%
• Headache	95%
• Myalgia	95%
• Nausea	62%
• Adenopathy	59%
• Splenomegaly	59%
• Rash	27%

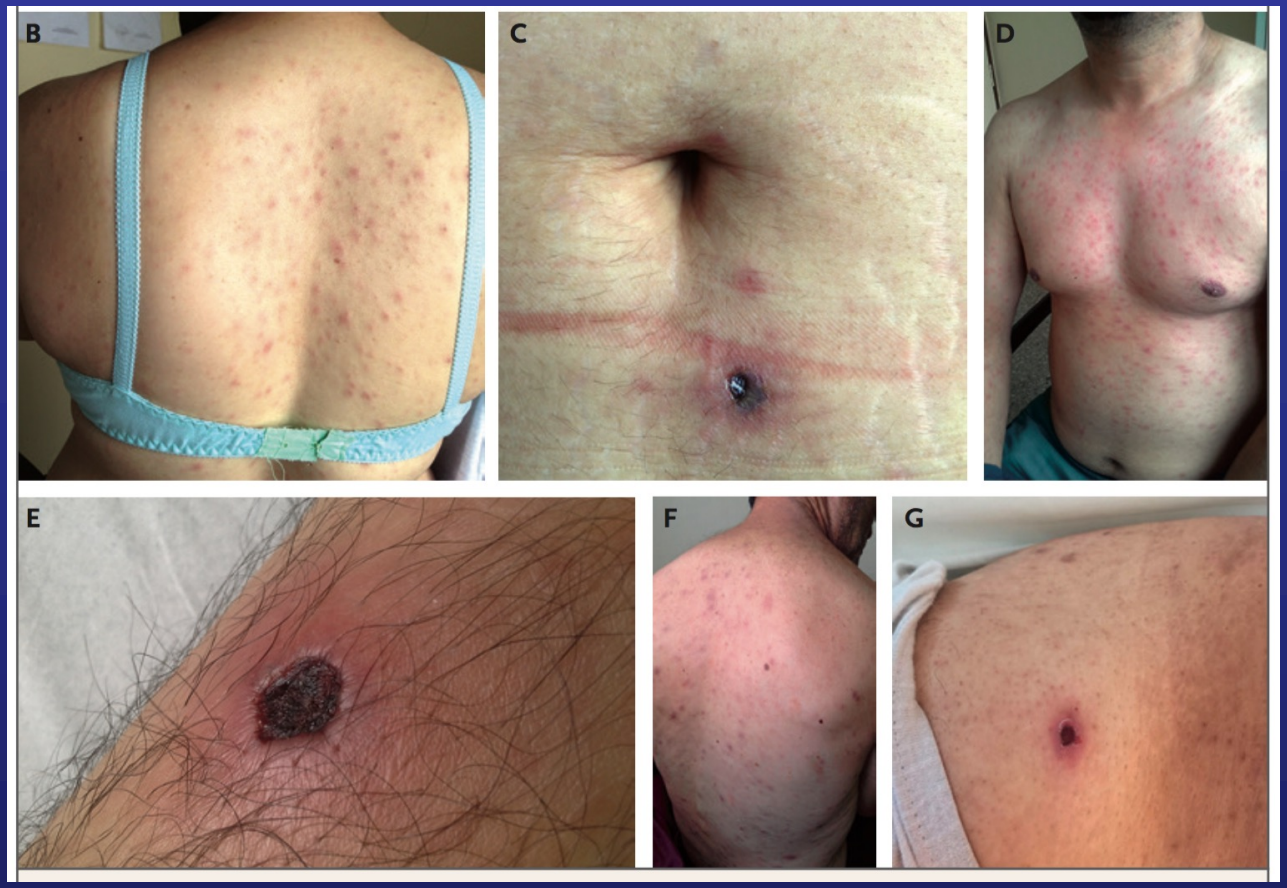
Scrub Typhus - Signs & Symptoms

- Eschar
  - Often with regional lymphadenopathy
  - Usually apparent by the time systemic symptoms appear
  - Often overlooked

- Can progress to cause:
  - Pneumonitis
  - Encephalitis
  - Shock

- Case fatality rate: 7 - 15%

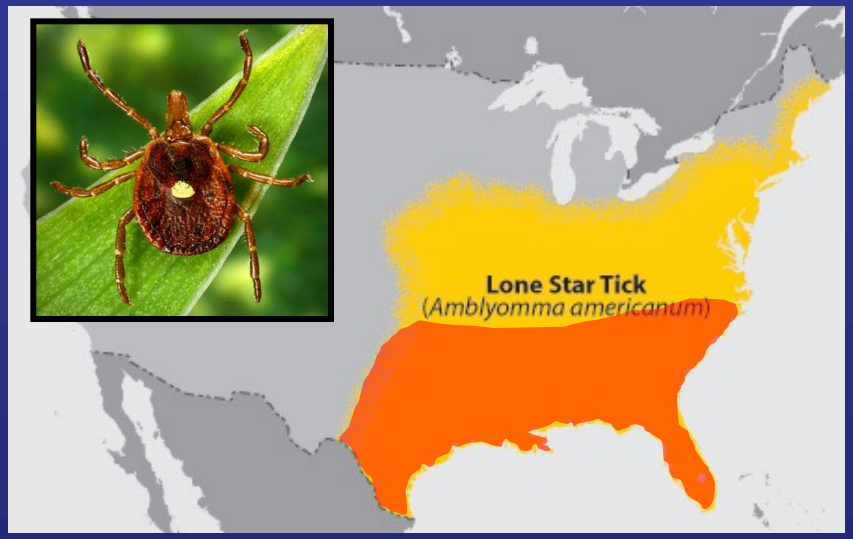
Scrub typhus in Chile – *Candidatus* Orientia Chiloensis



Weitzel et al. Endemic scrub typhus in South America. NEJM. 2016;375:954-961.
Weitzel et al. Scrub typhus in continental Chile, 2016-2018. EID. 2019;25:1214-1217.

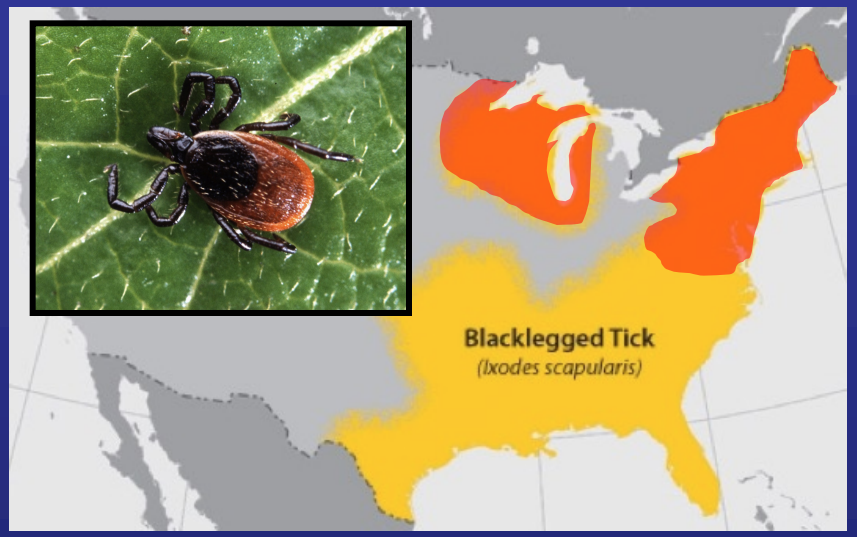
Ehrlichiosis and Anaplasmosis

Ehrlichia chaffeensis: Human monocytotropic ehrlichiosis



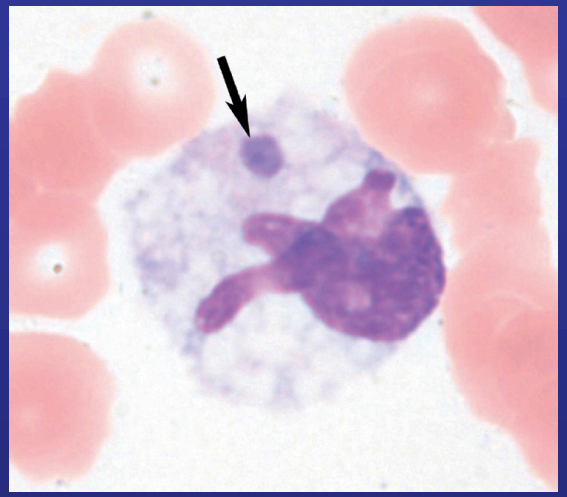
- Transmitted by *A. americanum*
- Occurs in southeast and southcentral U.S.
- Also occurs in Africa, South America, and Eastern Asia

Anaplasma phagocytophilum: Human granulocytotropic anaplasmosis



- Transmitted by *I. scapularis*
- Occurs in northeast and upper midwest U.S.
- Also occurs in northern Europe and Asia

Ehrlichia chaffeensis: Human monocytotropic ehrlichiosis

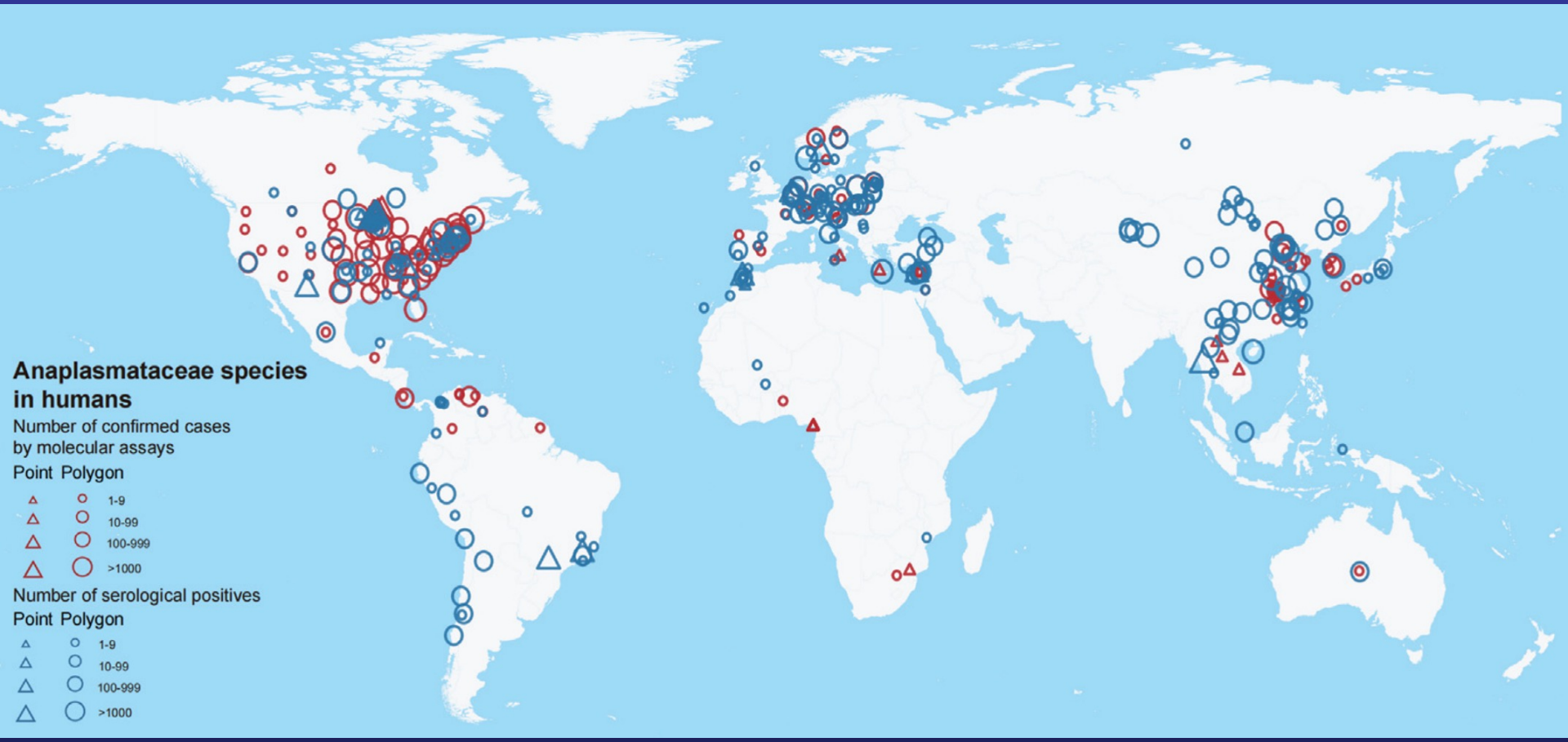


- Rash in ~ 35%
- Elevated transaminases, thrombocytopenia, and leukopenia frequent

Anaplasma phagocytophilum: Human granulocytotropic anaplasmosis

- Rash in < 10%
- Elevated transaminases, thrombocytopenia, and leukopenia frequent

Confirmed Cases of Infection with Anaplasmataceae



Huang et al. The Global Distribution and Risk Prediction of Anaplasmataceae species. eBioMed 2025;115:105722

Diagnosis

Diagnosis

- Do not wait for laboratory confirmation to start therapy
- Serology
  - Most available diagnostic method for clinicians
- PCR
  - Not sensitive from blood for rickettsioses
  - More sensitive from tissue (eschar or rash) specimens
  - Better sensitivity for ehrlichiosis and anaplasmosis
- Isolation and Immunohistochemistry
  - Only available in the research setting

Serologic Diagnosis

- Diagnosis is retrospective
  - Antibodies rarely detected in first week of illness
- IFA for IgG is the gold standard
- Definitive serologic diagnosis:
  - Seroconversion from acute- and convalescent-phase sera
  - 4-fold titer increase from acute- and convalescent-phase sera
- Single serum samples are problematic
  - Reactive specimens could represent old infection
  - Non-reactive specimens occur during early disease

Serologic Diagnosis

- Antibodies to SFG antigens cross react with other SFG antigen
  - e.g., anti-*R. africae* serum reacts against *R. rickettsii* antigen
- Antibodies to typhus group antigens cross react with other typhus group antigen
  - e.g., anti-*R. prowazekii* serum reacts against *R. typhi* antigen
- Antibodies to *Orientia* cross react variably to antigen of heterologous strains
- *Anaplasma* and *Ehrlichia* serology is separate but there may be some variable to weak cross reactivity

Treatment

Treatment Summary

	Doxycycline	Chloramphenicol*	Quinolones	Azithro	Rifampin
RMSF	Preferred	Alternative			
Typhus	Preferred	Alternative			
Murine typhus	Preferred	Alternative	Alternative? (+/-)	Alternative? (+/-)	
Other SFG *Rickettsia*	Preferred	Alternative	Alternative? (+/-)	Alternative? (+/-)	
Scrub typhus	Preferred	Alternative		Alternative	Alternative
Ehrlichia / *Anaplasma*	Preferred				Alternative

* Not available in the U.S.

Treatment

Severe infections caused by *Rickettsia* species
(RMSF and louse-borne epidemic typhus)

- Doxycycline 100 mg oral BID X 7 days
- Chloramphenicol 50 - 75 mg/kg/day X 7 days

Less severe infections caused by *Rickettsia* species
(other SFGR and murine typhus)

- Doxycycline 100 mg oral BID X 7 days
- Chloramphenicol 50 - 75 mg/kg/day X 7 days
- Ciprofloxacin 500 BID or levofloxacin 500 QD X 7 days

Treatment

Scrub typhus

- Doxycycline 100 mg oral BID X 7 days
- Chloramphenicol 50 - 75 mg/kg/day X 7 days
- Azithromycin 500 mg X 3 days

Anaplasmosis / Ehrlichiosis

- Doxycycline 100 mg oral BID X 7 - 14 days
- Rifampin 300 mg oral BID X 7 - 10 days

Treatment: Tetracyclines

- Minocycline is as effective as doxycycline
- Tetracycline hydrochloride has more GI intolerance
- Short courses of doxycycline are safe for children
- Doxycycline appears safe in pregnancy and doesn't seem to have adverse effects on developing fetus
- True doxycycline allergy is exceedingly uncommon

Susceptibility to Parenteral Tetracycline-like Agents

TABLE 1 Activities of eravacycline, omadacycline, and tigecycline against 10 rickettsial species

	MIC (μg/ml)			
Species or strain[a]	**Eravacycline**	**Omadacycline**	**Tigecycline**	**Doxycycline**
Rickettsia africae	≤0.06	0.5	0.5	≤0.06
Rickettsia australis	≤0.06	0.5	1.0	≤0.06
Rickettsia conorii India tick typhus strain	≤0.06	0.5	0.5	≤0.06
Rickettsia conorii Malish 7 strain	≤0.06	1.0	1.0	≤0.06
Rickettsia honei	≤0.06	1.0	0.5	0.13
Rickettsia parkeri	≤0.06	0.5	0.5	0.13
Rickettsia rickettsii	≤0.06	1.0	0.5[b]	0.13
Rickettsia sibirica	≤0.06	1.0	1.0	≤0.06
Rickettsia slovaca	≤0.06	2.0	1.0	0.13
Rickettsia typhi	≤0.06	0.5	1.0	≤0.06
MIC_{50}[c]	≤0.06	0.5	0.5	≤0.06
MIC_{90}[c]	≤0.06	1.0	1.0	0.13

Quade BR, et al. In vitro susceptibility of Rickettsia species to eravacycline, omadacycline, and tigecycline. Antimicrobial Agents and Chemotherapy 2021; 65: e00665-21

Thank You

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