

ESCMID Postgraduate Technical Workshop
 Intracellular bacteria: from biology to clinic
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Flea-, louse and mite-borne rickettsioses



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Rickettsioses

✓ Vary greatly from mild, self-limiting, to life-threatening diseases

Mortality


0 % (*R. slovaca*, *R. africae*, *R. felis*)
 ↓
 1% (*R. typhi*)
 ↓
 2 % (*R. conorii*, *R. rickettsii*)
 ↓
 20% (*R. prowazekii*)



Differences in pathogenicity

Role of genome decay on virulence?

Virulence linked to genome reduction



Gene covered by 11 annotated Rickettsia	11	10	9	8	7	6	5
11 genes	100%	100%	100%	100%	100%	100%	100%
10 genes	90%	90%	90%	90%	90%	90%	90%
9 genes	80%	80%	80%	80%	80%	80%	80%
8 genes	70%	70%	70%	70%	70%	70%	70%
7 genes	60%	60%	60%	60%	60%	60%	60%
6 genes	50%	50%	50%	50%	50%	50%	50%
5 genes	40%	40%	40%	40%	40%	40%	40%
4 genes	30%	30%	30%	30%	30%	30%	30%
3 genes	20%	20%	20%	20%	20%	20%	20%
2 genes	10%	10%	10%	10%	10%	10%	10%
1 gene	0%	0%	0%	0%	0%	0%	0%

- ✓ *R. africae* genome
- ✓ 1,27 Mb chromosome
- ✓ 1 unstable plasmid
- ✓ Highly clonal
- ✓ The most virulent species has the smallest genome
- ✓ Loss of regulatory genes

Analysis of the *Rickettsia africae* genome reveals that virulence acquisition in *Rickettsia* species may be explained by genome reduction
 Pierre-Edouard Fournier¹, Khalid El Khatib², Quentin Leroy³, Catherine Robert⁴, Bernadette Gastaldello⁵, Patricia Benoit⁶, Céline Socorro⁷, Philippe Faudou⁸, Stéphane Audic⁹ and Didier Raouich^{1,11}
 BMC GENOMICS 2010, 11:141

An isolated phenomenon?

Species	genome size (bp)	GC (%)	coding %	ORFs	paralogues	phages	order/family
<i>M. leproae</i>	3,206,201	57%	49%	1625	1112	0	Actinobacteria / Microthriciales
<i>M. goodii</i>	3,426,201	68%	58%	5120	1148	0	Actinobacteria / Microthriciales
<i>M. indicus-pruriens</i>	4,411,532	65%	56%	3848	8	0	Actinobacteria / Microthriciales
<i>M. indicus</i>	8,906,280	67%	56%	4750	168	0	Actinobacteria / Microthriciales
<i>M. neoaurum</i>	1,151,520	29%	75%	835	0	0	Proteobacteria / Rhodospirillales
<i>R. africae</i>	1,278,840	32%	72%	1030	87	0	Proteobacteria / Rickettsiales
<i>R. sibirica</i>	2,426,635	31%	66%	2252	48	0	Actinobacteria / Comamonadales
<i>C. elkhartiense</i>	3,114,170	34%	66%	3052	0	0	Actinobacteria / Comamonadales
<i>S. typhus</i>	1,126,420	27%	83%	1028	0	0	Spirochaetes / Spirochaetales
<i>Y. pestis</i>	2,832,201	57%	91%	2767	19	0	Proteobacteria / Yersiniaceae
<i>Y. pseudotuberculosis</i>	4,744,671	47%	82%	3901	71	0	Proteobacteria / Yersiniaceae
<i>B. pertussis</i>	4,086,109	67%	82%	3436	388	0	Proteobacteria / Borreliales
<i>B. burgdorferi</i>	5,200,170	68%	91%	4984	12	0	Proteobacteria / Borreliales
<i>S. pneumoniae</i>	2,076,201	39%	63%	2145	0	0	Firmicutes / Lactobacillales
<i>S. saprophyticus</i>	1,160,207	35%	66%	2124	0	0	Firmicutes / Lactobacillales
<i>S. dysgalactiae</i>	1,526,202	38%	66%	1896	0	0	Firmicutes / Lactobacillales
<i>S. mitis</i>	1,086,200	41%	66%	2186	0	0	Firmicutes / Lactobacillales
<i>S. Typhimurium</i>	4,806,037	52%	63%	4781	205	0	Proteobacteria / Yersiniaceae
<i>S. Schwarzengrund</i>	4,760,075	52%	65%	4502	152	0	Proteobacteria / Yersiniaceae
<i>S. dysenteriae</i>	4,349,232	51%	70%	4270	284	0	Proteobacteria / Yersiniaceae
<i>E. coli</i> O157	4,845,518	50%	88%	4719	0	0	Proteobacteria / Yersiniaceae
<i>Y. enterocolitica</i> o/e1	3,138,320	46%	86%	1135	0	0	Proteobacteria / Yersiniaceae
<i>Y. enterocolitica</i> o/e2	3,024,669	47%	88%	2742	1	0	Proteobacteria / Yersiniaceae
<i>Y. pseudotuberculosis</i> o/e1	3,288,538	45%	86%	3080	0	0	Proteobacteria / Yersiniaceae
<i>Y. pseudotuberculosis</i> o/e2	3,177,212	45%	86%	1752	0	0	Proteobacteria / Yersiniaceae


Genomes of the Most Dangerous Epidemic Bacteria Have a Virulence Repertoire Characterized by Fewer Genes but More Toxin-Antitoxin Modules
 BMC GENOMICS 2011, 12:143

Differences in pathogenicity

May differences among species explain everything?


Pathogenesis of rickettsial infections

Host-associated factors




Worse outcome

- ✓ Age > 40 years (RMSF), > 60 years (MSF)
- ✓ Male sex (Δ occupational bias)
- ✓ Ethnical factors: Native Americans (reduced access to healthcare facilities)
- ✓ Comorbidities: Chronic alcoholism, diabetes
- ✓ Genetic background: deficit in G6PD
mutated TLR-4




Pathogenesis of rickettsial infections

Impact of treatment



Worse outcome

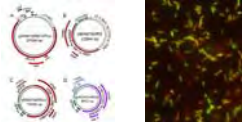

- ✓ Delayed diagnosis and treatment
- ✓ Cotrimoxazole, chloramphenicol in MSF and ET
- ✓ Fluoroquinolones in ET, MT, MSF



Few answers, many questions

- ✓ Pathogenesis only partially known
- ✓ Virulence of rickettsiae is multi-parametric
- ✓ Adhesion to host cells crucial (SCA proteins)
- ✓ Host factors play a significant role
- ✓ Comparative genomics may help identify virulence factors
- ✓ Role of T4SS?
- ✓ Role of toxin-antitoxin modules?

Development of Stable Vectors for Transinfection of Disease Rickettsial Species
Journal of Eukaryotic Microbiology, Volume 12, Issue 1, December 2011

Flea-transmitted rickettsioses

Worldwide diseases



Flea-transmitted diseases

- ✓ *R. felis*
- ✓ *R. typhi*
- ✓ *B. henselae*
- ✓ *B. quintana?*
- ✓ *Y. pestis*



Fleas



Fleas



Murine typhus

- ✓ *Rickettsia typhi* (*R. mooseri*)
- ✓ Vector : rat fleas (*X. cheopis*), cat fleas, mouse fleas
- ✓ Reservoir: rats, cats, opossums
- ✓ Infection by flea feces
- ✓ Prevalent in southern USA, Hawaii, central and south America, Africa, Asia (Indonesia), Mediterranean area (Greece, Cyprus, Spain, North Africa)
- ✓ Fever, headache, arthro-myalgias, MP rash (40 - 50 %)
- ✓ Neurological signs such as confusion, stupor, seizures or imbalance (up to 45%)
- ✓ Mostly mild. Deadly in elderly and immunocompromised patients without treatment



Flea spotted fever

- ✓ *Rickettsia felis*
- ✓ In 1970, changing distribution of murine typhus
- ✓ Cases in the rich Orange county (CA)
- ✓ Opossums = major actors
- ✓ Infested by cat fleas (*C. felis*)
- ✓ Fever (100%), MP or vesicular rash (90%), eschar (variable depending on country)



(Raoult *et al.* Emerg Infect Dis. 2001)



Flea spotted fever

- ✓ Triad fever + eschar + rash = "Yaaf" in Africa (febrile vesicular rash with eschar) Mediannikov *et al.* J Infect. 2013;66:536-40
- ✓ Photophobia, hearing loss, and signs of meningitis (rare)
- ✓ Mostly mild

- ✓ USA, Brazil, Mexico, Germany, France, Australia, Algeria

- ✓ High seroprevalence in Senegal and Kenya (51 and 57% of febrile patients, respectively) Maina *et al.* Emerg Infect Dis. 2012;18:328-31



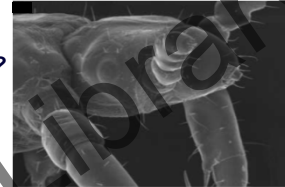
- ✓ Role of *Anopheles* and *Aedes* mosquitoes in Africa (similar epidemiology to malaria) Socolovschi *et al.* PLOS One. 2012;7:e48254



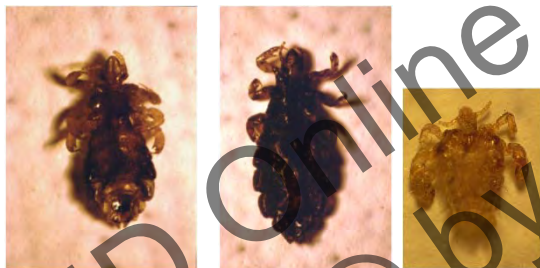
Louse-transmitted rickettsioses

Louse transmitted bacteria

- ✓ *Rickettsia prowazekii*
- ✓ *Borrelia recurrentis*
- ✓ *Bartonella quintana*
- ✓ *Acinetobacter baumannii?*

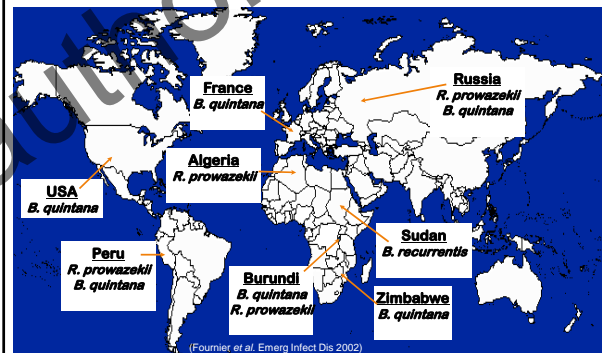


Human lice



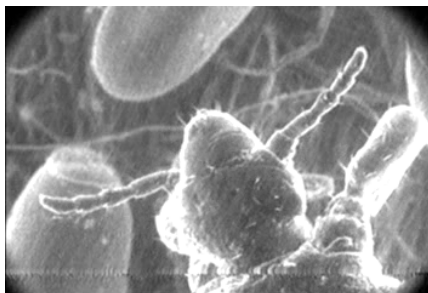
Pediculus humanus capitis *Pediculus humanus humanus* *Phtirus pubis*

Pediculus humanus humanus -transmitted bacteria



(Fournier et al. Emerg Infect Dis 2002)

Pediculus humanus humanus



Blood meal on a healthy volunteer

- ✓ *P.h.humanus* only bites humans (except Culpepper)
- ✓ Only blood meal
- ✓ 5 meals/d
- ✓ Highly sensitive to heat and dessication



***P. h. humanus* lives
In clothes**



**Epidemic typhus,
Reemerging disease**

- ✓ 1990-1992: Isolated cases in Ethiopia and Nigeria
(Perine et al. Clin. Infect. Dis. 1992)
- ✓ 1990-1993: Isolated cases in Peru
(WHO memorandum. Bull. World Health Organ. 1993)
- ✓ 1993 : Civil war in Burundi and Rwanda
- ✓ 1994 : 800,000 Rwandan refugees in Goma, Zaire
- ✓ Louse outbreak but no typhus
- ✓ 1995: outbreak in a jail in Burundi: 9 cases
(Raoult et al. Emerg. Infect. Dis. 1997)
- ✓ 1996-1997: Outbreak in refugee camps in Burundi
> 45,000 cas
(Raoult et al. Lancet. 1998)
- ✓ 2004: Isolated case in Algeria
(Mokram et al. J. Clin. Microbiol. 2004)



**Epidemic typhus
(Jail fever, Red louse fever)**



- ✓ *Rickettsia prowazekii*
- ✓ Vector : only *P. h. humanus* (not *capitis*)
- ✓ Fever - rash : 30 - 60 %
- ✓ Myalgia ++ ("sutama")
- ✓ Headache, obtubilation ("tuphos")
- ✓ 10-30% mortality without treatment
- ✓ Treatment : unique dose of 200 mg doxycycline



(Houhamdi et al. J. Infect. Dis. 2002)



**Epidemic typhus in USA
Role of flying squirrels (1975)**

- ✓ *R. prowazekii* associated to squirrel lice
- ✓ East and West USA
- ✓ Less severe



**Detection of *R. prowazekii*
in ticks**



1966: *Amblyomma* in Africa
Reiss-Gutfreund RJ. 1966. Am J Trop Med Hyg; 15: 943-49.

2005: *Amblyomma* in Mexico in 2005
Medina-Sanchez A., et al. 2005. Ann N Y Acad Sci; 1063:327-32.

Role in epidemiology?



**Mite-transmitted
rickettsioses**



Rickettsialpox

- ✓ *Rickettsia akari*
- ✓ Vector = *Allodermanyssus sanguineus* (mouse mite)
- ✓ Prevalent in USA, Ukraine, Slovenia, Korea
- ✓ Fever, rash (vesicular)
Eschar, regional lymph nodes
- ✓ Mild
- ✓ New York + + +
- ✓ High seroprevalence in Baltimore drug addicts
- ✓ Under high surveillance since 9-11, 2001 (eschar ~ smallpox)



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