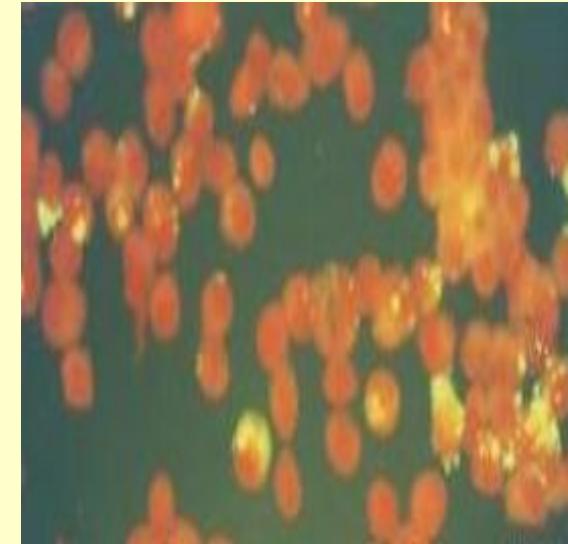
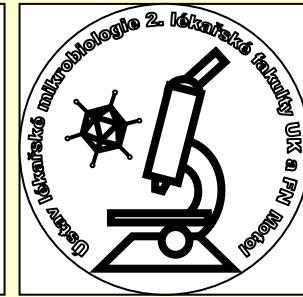




Classification of Bartonella species and pathogenesis of infections



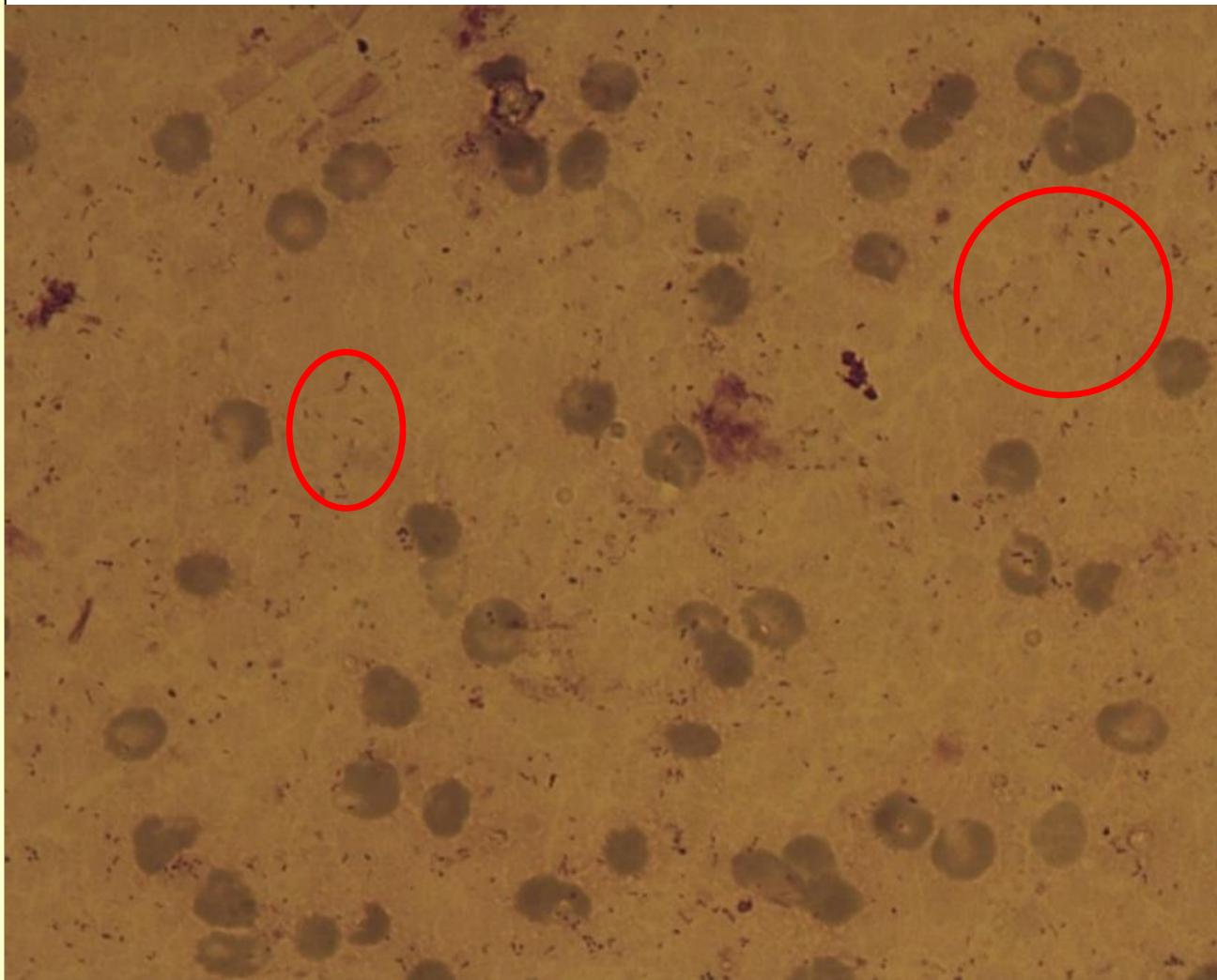
Oto Melter

Department of Medial Microbiology, 2nd Faculty of Medicine
Charles University
Prague

Original characteristics of *Bartonella* genus

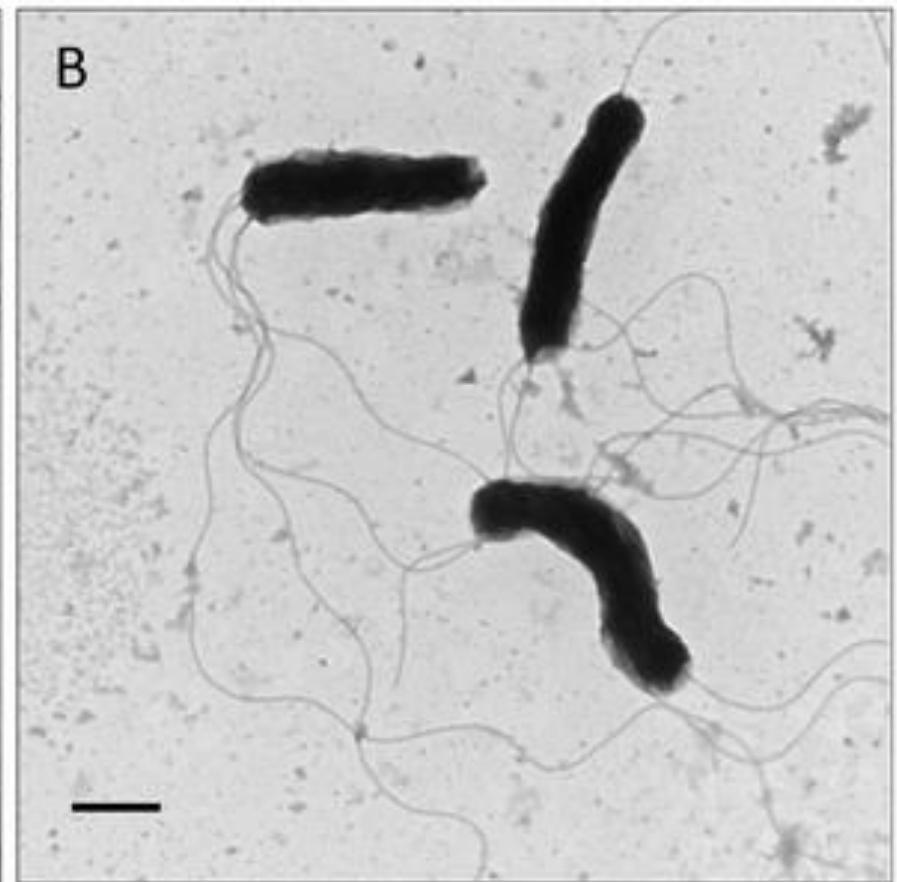
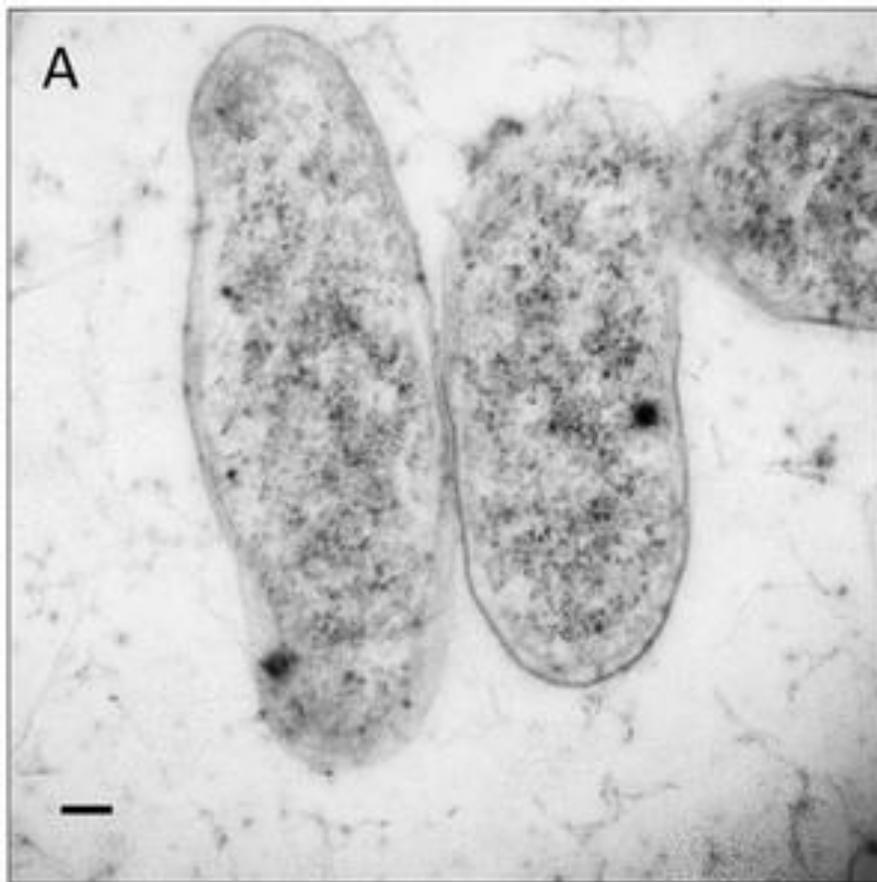
1. Agents of *emerging* and *re-emerging* infections
2. Small genome size (<2 Mb)
3. Intracellular & hemotropic
4. Long generation time & culture & identif./diagnosis
5. Long-term antibiotic treatment

Bartonella morphology – light microscopy



Gram-rods or **coccobacilli** can be seen on preparation from heart valve of patient with endocarditis caused by *Bartonella quintana* (Melter unpublished)

Bartonella morphology – electron microscopy



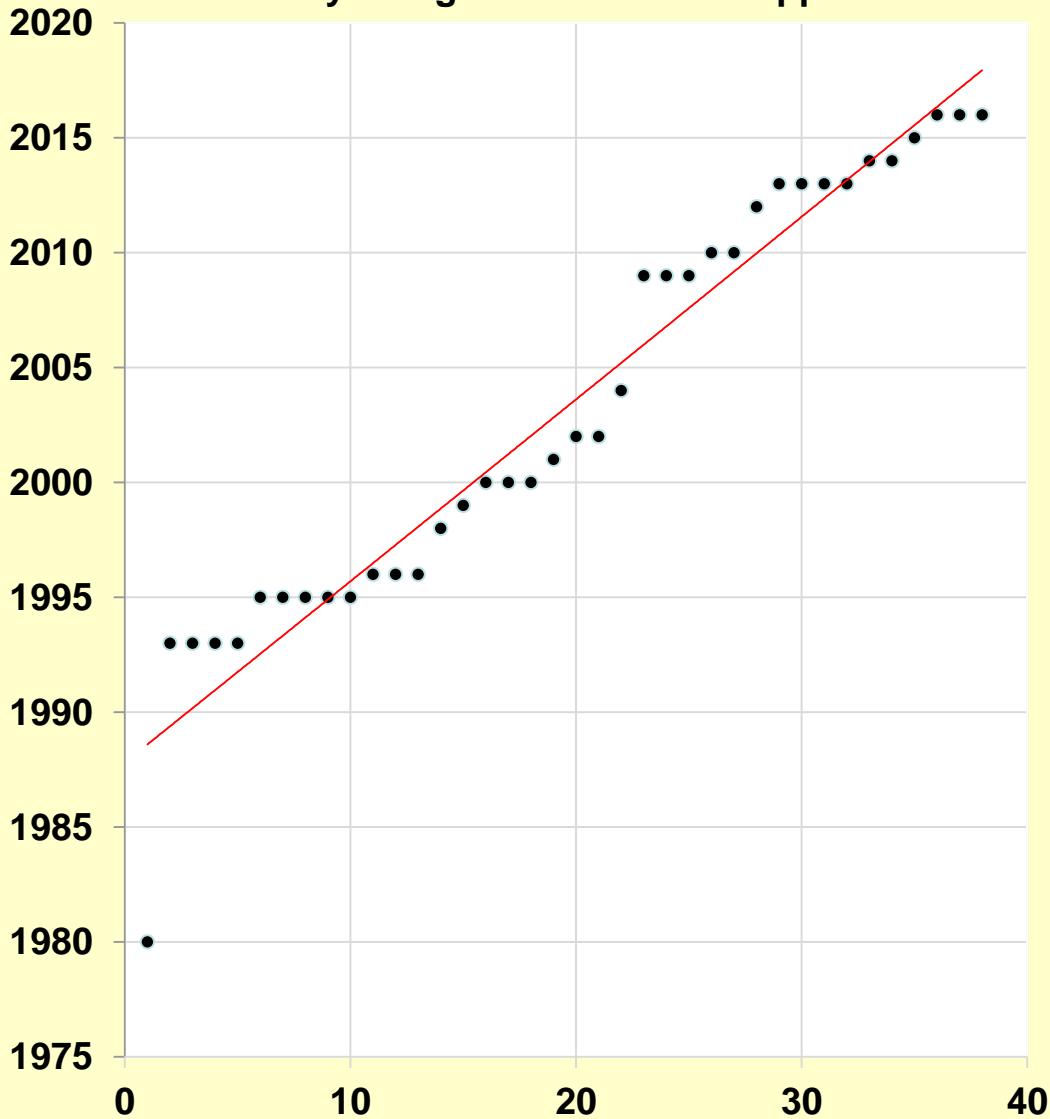
Lophotrichous flagella of *B. bacilliformis*

Bartonella taxonomy

- Alpha 2 subgroup of the phylum **Proteobacteria**, order **Rhizobiales**, family **Bartonellaceae**, since 1993 removed from order Rickettsiales where was included together with Rickettsiaceae and Anaplasmataceae (*Brenner DJ et al.*)
- Gram- negative rods, GC content ~ 40%, closest genera **Brucela**, **Rhizobium**, **Agrobacterium**
- Today 36 validly described species (*Euzéby, List of prokaryotic names, 2017*), 51 including **Candidatus species** and still dont approved species (a few hundred *Bartonella* spp. strains, NCBI database)
- Except *B. bacilliformis* exist **modern bartonellae**, which **evolved** probably by **adaptation** to mammals as reservoir by **retraction of its genome** or by the **acquisition of various phage-related elements**

Emergence of new Bartonella species

Newly recognized *Bartonella* spp.

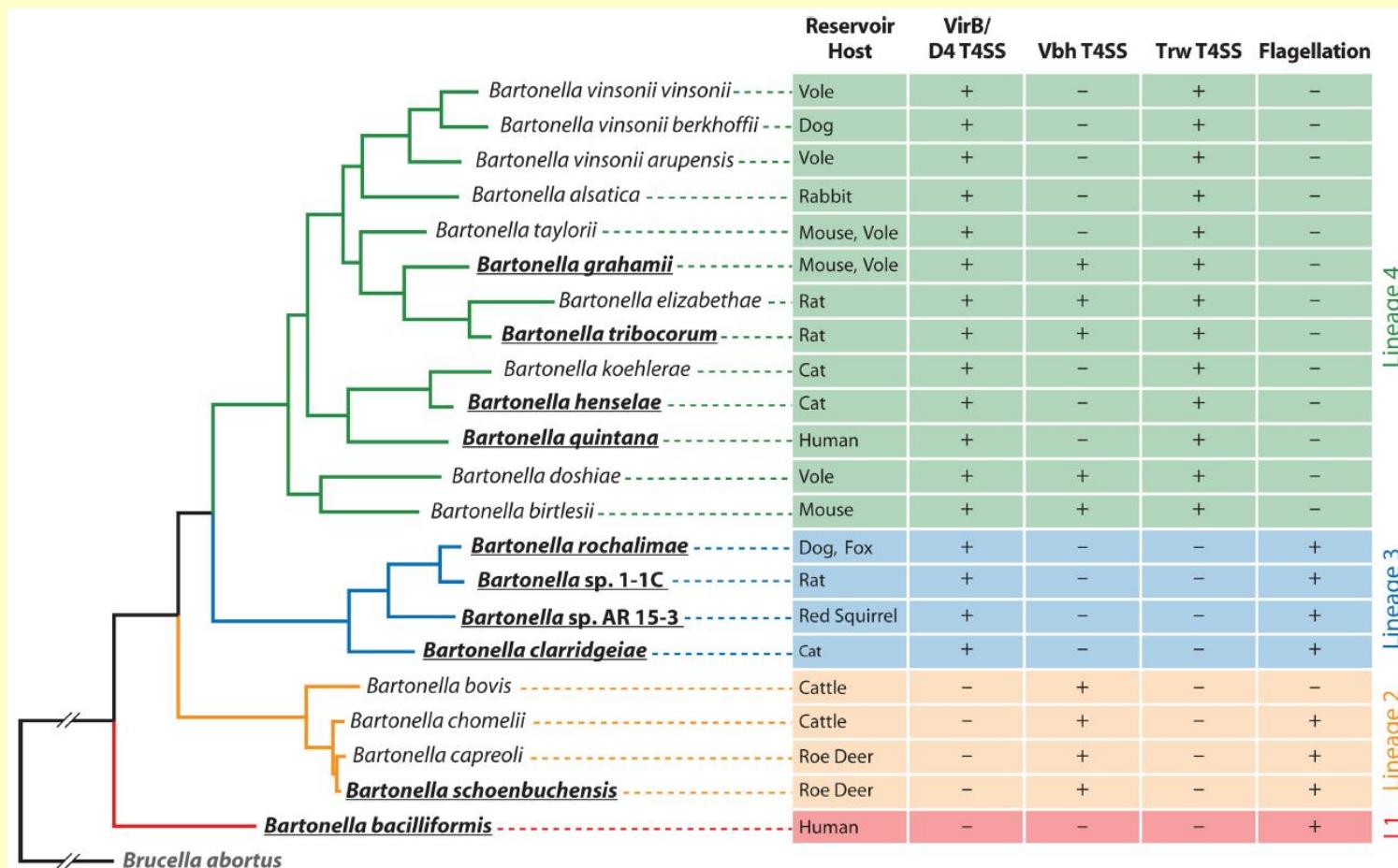


No year species (Euzeby, 1.9.2017)

author	species
Strong et al.	1 1980 <i>Bartonella bacilliformis</i>
Schmincke	2 1993 <i>Bartonella quintana</i>
Weiss and Dasch	3 1993 <i>Bartonella vinsonii</i>
Regnery et al.	4 1993 <i>Bartonella henselae</i>
Daly et al.	5 1993 <i>Bartonella elizabethae</i>
Ristic and Kreier	6 1995 <i>Bartonella peromysci</i>
Ristic and Kreier	7 1995 <i>Bartonella talpae</i>
Birtles et al.	8 1995 <i>Bartonella doshiae</i>
Birtles et al.	9 1995 <i>Bartonella grahamii</i>
Birtles et al.	10 1995 <i>Bartonella taylorii</i>
Weiss and Dasch	11 1996 <i>Bartonella vinsonii</i> subsp. <i>vinsonii</i>
Lawson and Collins	12 1996 <i>Bartonella clarridgeiae</i>
Kordick et al.	13 1996 <i>Bartonella vinsonii</i> subsp. <i>berkhoffii</i>
Heller et al.	14 1998 <i>Bartonella tribocorum</i>
Heller et al.	15 1999 <i>Bartonella alsatica</i>
Bermond et al.	16 2000 <i>Bartonella birtlesii</i>
Droz et al.	17 2000 <i>Bartonella koehlerae</i> <i>Bartonella vinsonii</i> subsp. 18 2000 <i>arupensis</i>
Welch et al.	19 2001 <i>Bartonella schoenbuchensis</i>
Bermond et al.	20 2002 <i>Bartonella bovis</i>
Bermond et al.	21 2002 <i>Bartonella capreoli</i>
Maillard et al.	22 2004 <i>Bartonella chomelii</i>
Gundi et al.	23 2009 <i>Bartonella coopersplainsensis</i>
Gundi et al.	24 2009 <i>Bartonella queenslandensis</i>
Gundi et al.	25 2009 <i>Bartonella rattaaustraliani</i>
Inoue et al.	26 2010 <i>Bartonella japonica</i>
Inoue et al.	27 2010 <i>Bartonella silvatica</i>
Eremeeva et al.	28 2012 <i>Bartonella rochalimae</i>
Sato et al.	29 2013 <i>Bartonella acomydis</i>
Sato et al.	30 2013 <i>Bartonella callosciuri</i>
Sato et al.	31 2013 <i>Bartonella jaculi</i>
Sato et al.	32 2013 <i>Bartonella pachyuromydis</i>
Mediannikov et al.	33 2014 <i>Bartonella florencae</i>
Mediannikov et al.	34 2014 <i>Bartonella senegalensis</i>
Mullins et al.	35 2015 <i>Bartonella ancashensis</i>
Kešnerová et al.	36 2016 <i>Bartonella apis</i>
Li et al.	37 2016 <i>Bartonella fuyuanensis</i>
Li et al.	38 2016 <i>Bartonella heixiaziensis</i>

Fylogenetic structure of *Bartonella* genus

(Maximum-likelihood analysis of close to 500 genes)

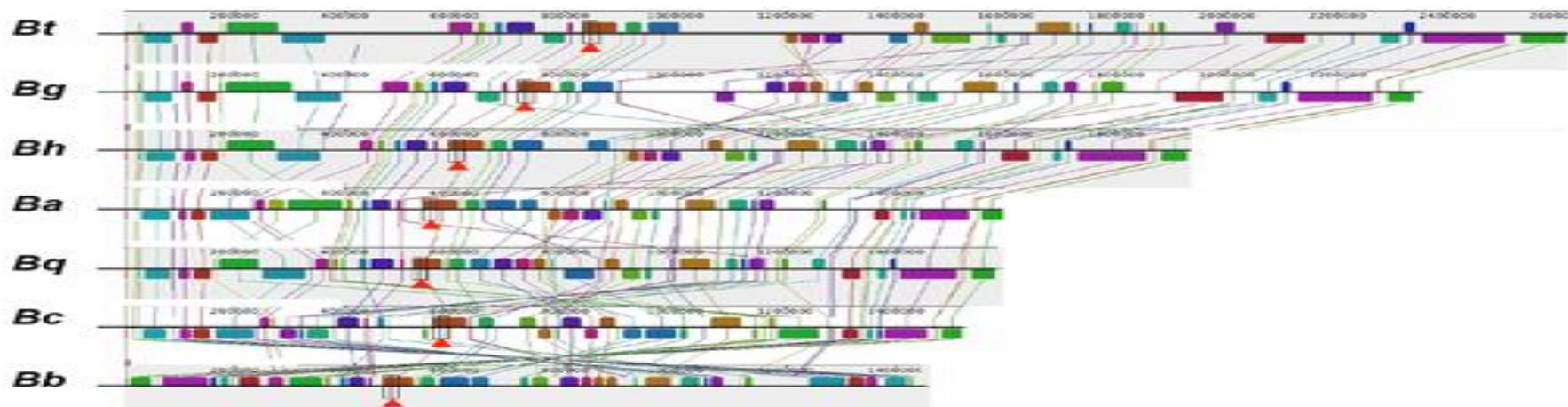


- L1 – original lineage & *B. bacilliformis*, absence of secretory system IV.
- L2 – L4 lineages & „modern“ *bartonellae*

Genomic structure of selected *Bartonella* chromosomes

A

	Chr (Mb)	Pla (Kb)	genes	proteins	GC%	fla	flaC/hecB	impA	trw	virB	vbh
<i>B. tribocorum</i>	2.64	23.3	2,166	2,087	38.9	○	●	○	●	●	○
<i>B. grahamii</i>	2.37	28.1	2,053	1,768	38.1	○	●	○	●	●	●
<i>B. henselae</i>	1.93	--	1,665	1,488	38.2	○	●	○	●	●	○
<i>B. australis</i>	1.6	--	1,313	1,264	41.8	○	○	●	●	○	●
<i>B. quintana</i>	1.58	--	1,356	1,142	38.8	○	○	○	●	●	○
<i>B. clarridgeiae</i>	1.52	--	1,445	1,323	35.7	●	○	○	○	●	○
<i>B. bacilliformis</i>	1.45	--	1,375	1,238	38.2	●	○	●	○	○	○

B

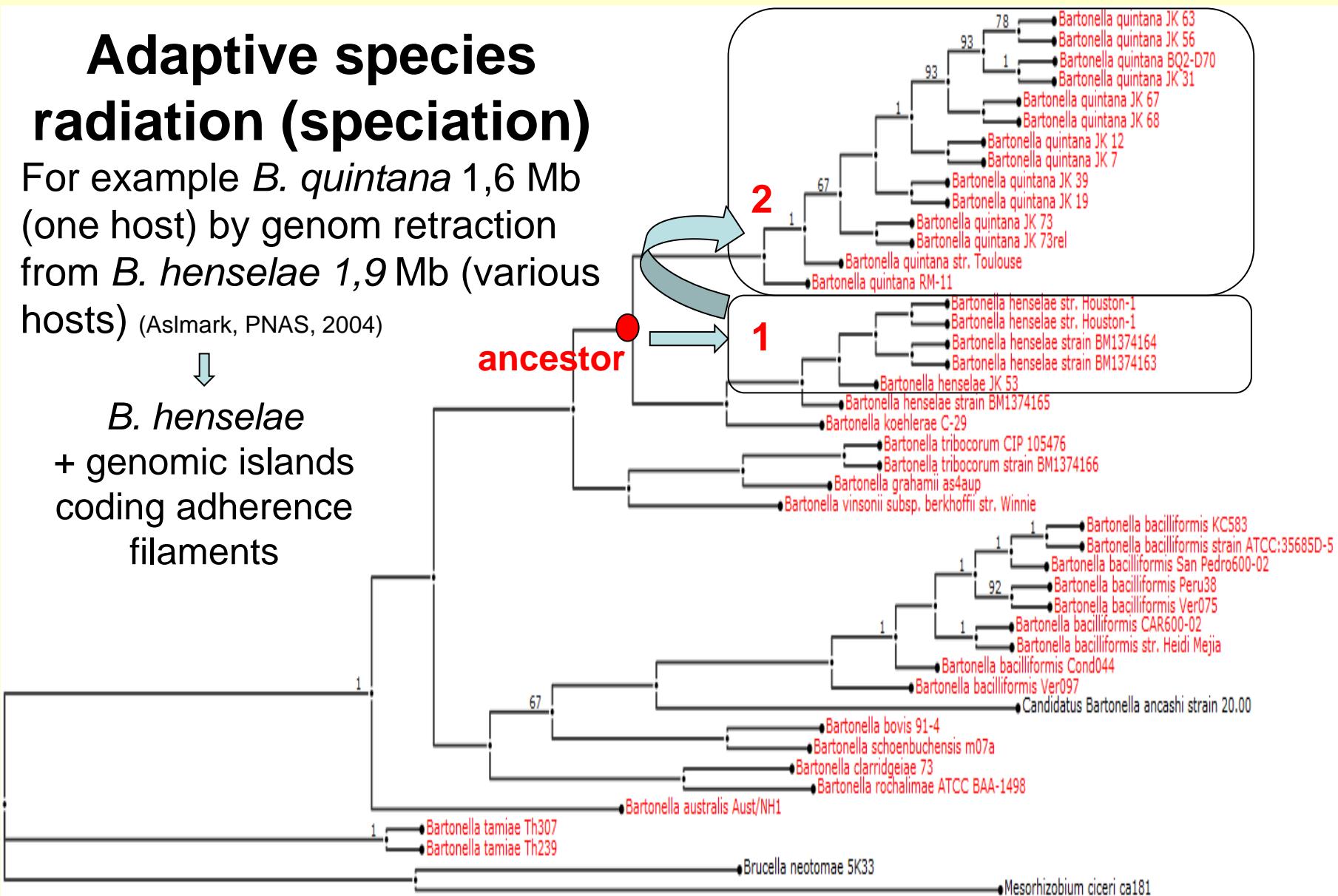
Phylogram (PATRIC database)

Adaptive species radiation (speciation)

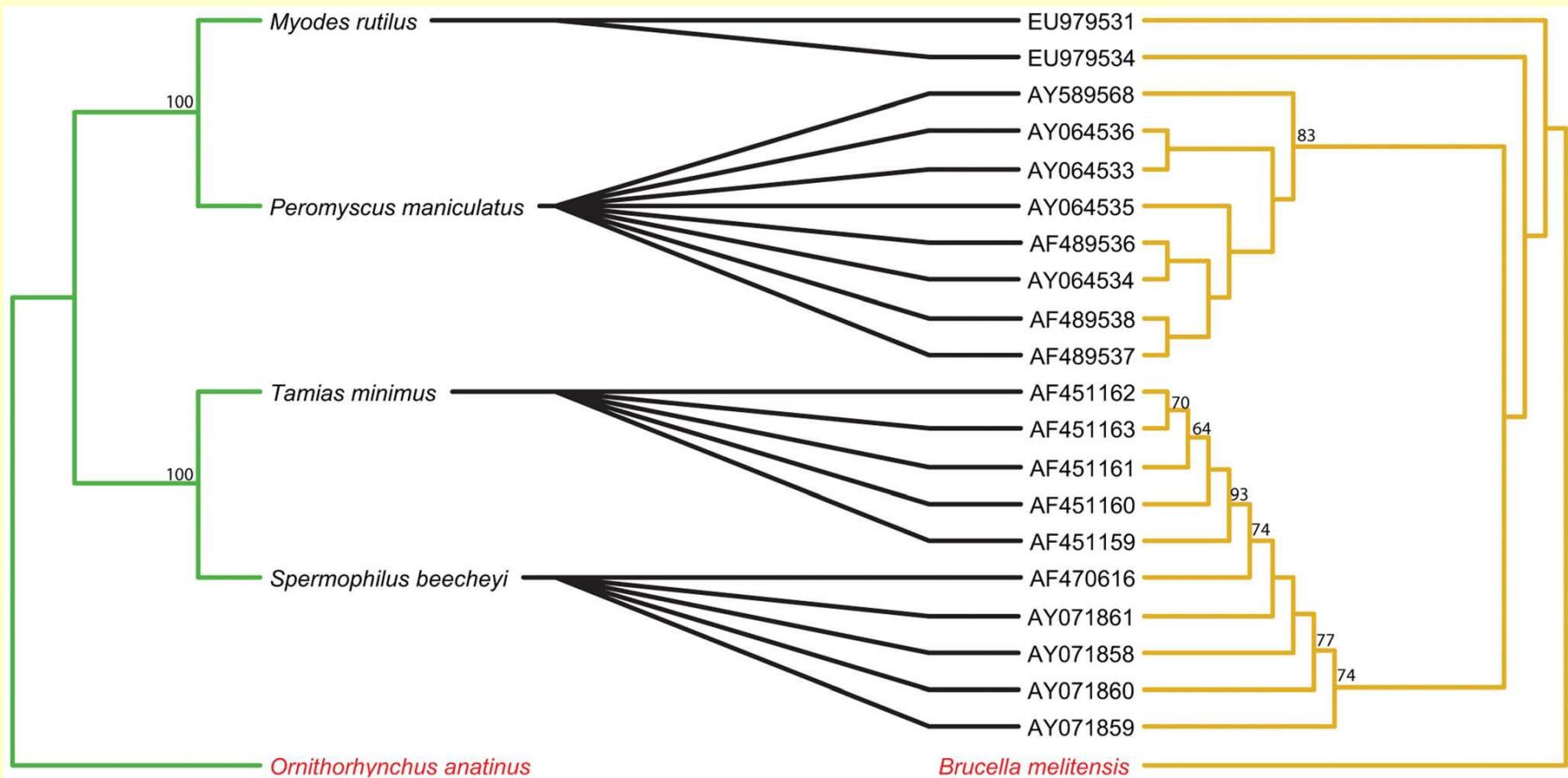
For example *B. quintana* 1,6 Mb (one host) by genome retraction from *B. henselae* 1,9 Mb (various hosts) (Aslmark, PNAS, 2004)



B. henselae
+ genomic islands
coding adherence
filaments



Significant coevolution/cospeciation with rodents and bats (Old & New World)

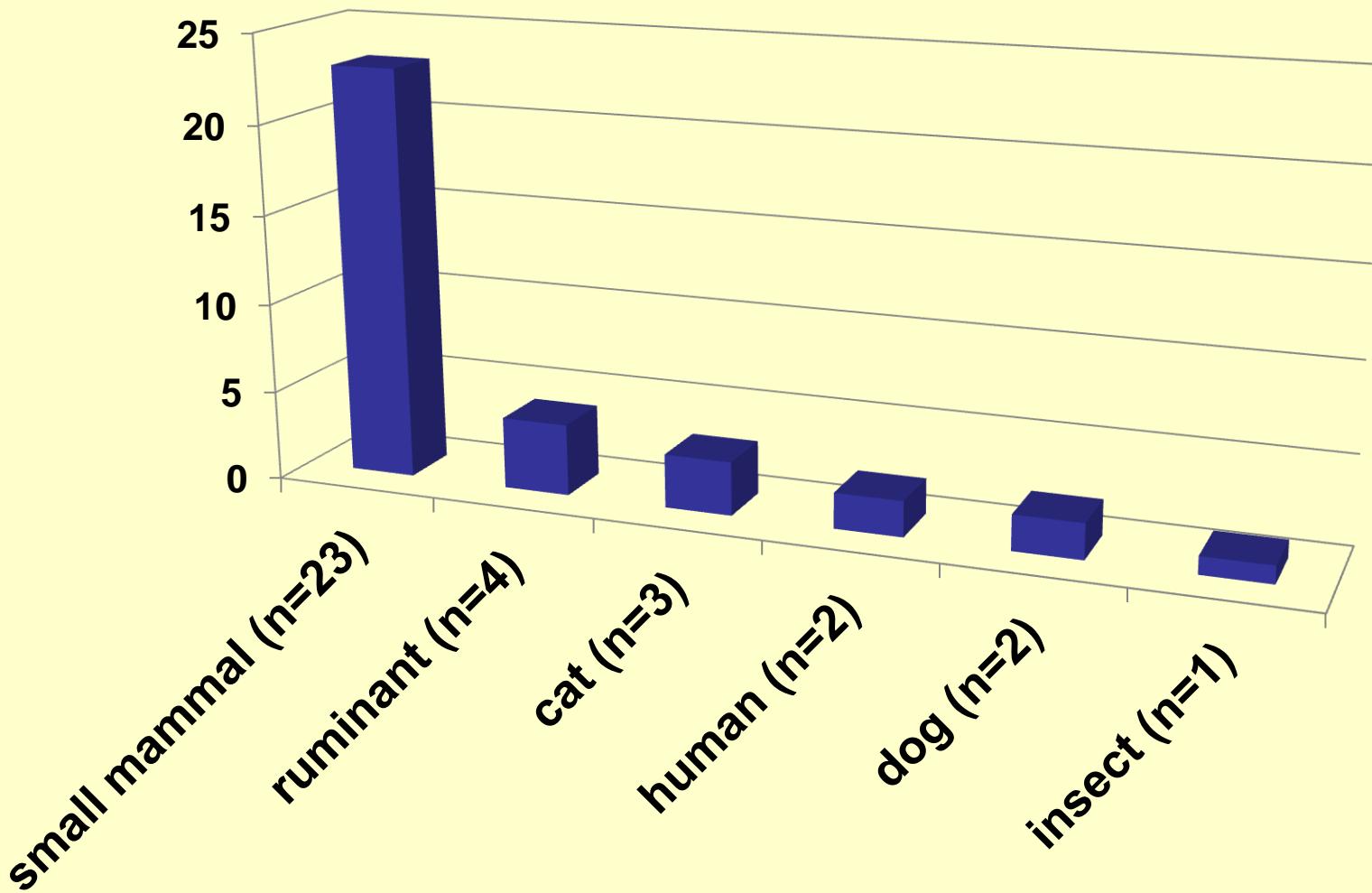


Example: **Tanglegram of cophylogenetic relationships between New World rodent hosts and Bartonella strains.** All host-pathogen associations are shown in the tanglegram as black connecting lines and are significant (Lei et al., PLOS, 2014)

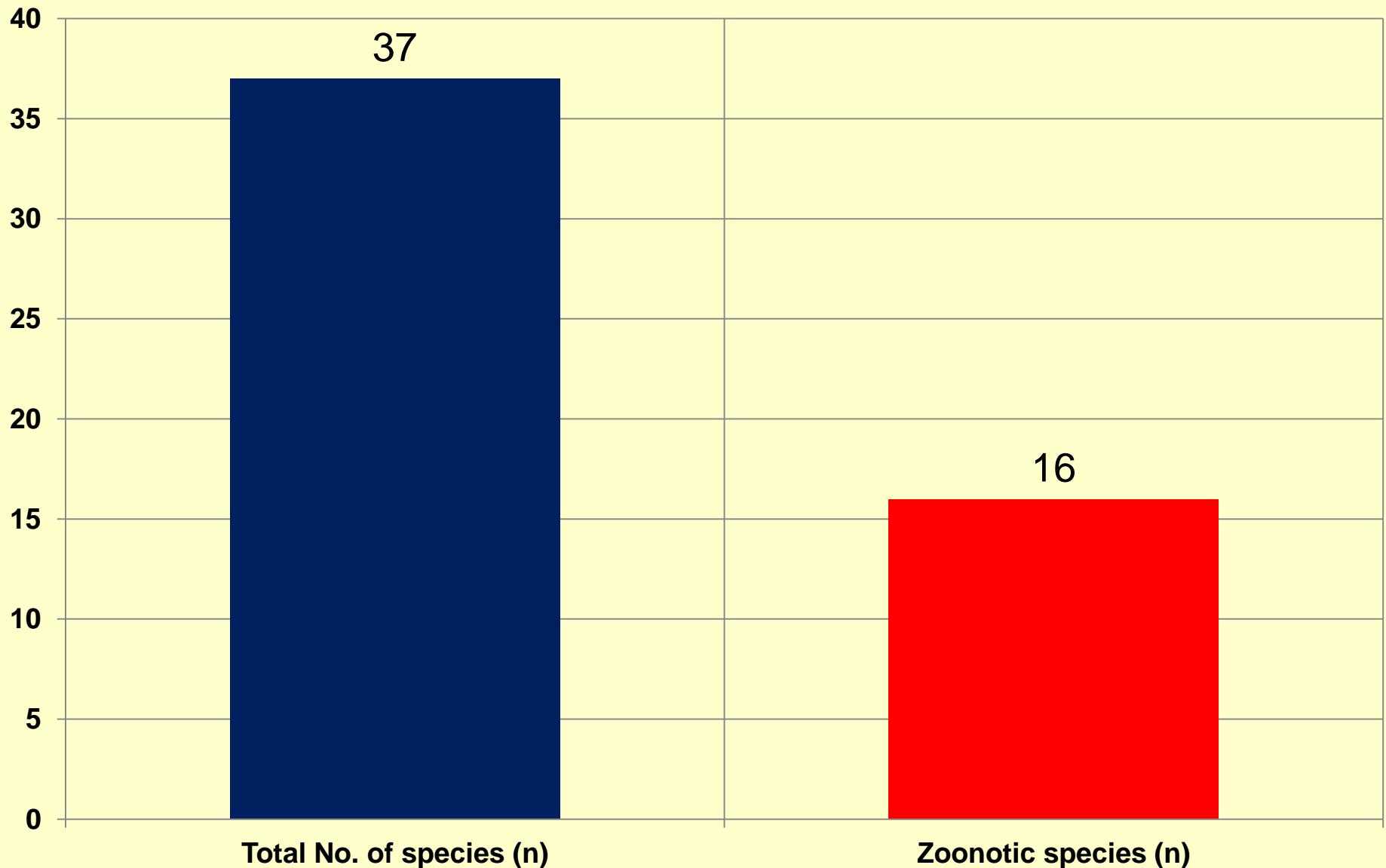
Others agents, reservoir & vectors

No	zoonosis	Species (Euzeby, 1.9.2017)	(potential) vector	host
1		<i>Bartonella acomydis</i>	unknown	small mammal
2	Endocarditis	<i>Bartonella alsatica</i>	(flea, ticks)	small mammal
3	Bacillary angiomatosis	<i>Bartonella ancashensis</i>	unknown (? <i>Lutzomyia</i>)	? Human
4		<i>Bartonella apis</i>	none	honey bee
5	Bacillary angiomatosis	<i>Bartonella bacilliformis</i>	<i>Lutzomyia verrucarum</i>	human
6		<i>Bartonella birtlesii</i>	fleas	small mammal
7???	Breitschwerdt	<i>Bartonella bovis</i>	(biting flies, ticks)	domestic ruminant
8		<i>Bartonella callosciuri</i>	unknown	small mammal
9		<i>Bartonella capreoli</i>	biting flies, ticks	wild ruminant
10		<i>Bartonella chomelii</i>	biting flies, ticks	domestic ruminant
11	Cat scratch disease	<i>Bartonella clarridgeiae</i>	(flea, ticks), cat attack	cat
12		<i>Bartonella cooperstaplainsensis</i>	(? fleas)	small mammal
13???	Only in Breitschw.	<i>Bartonella doshiae</i>	(? fleas)	small mammal
14	Endocarditis	<i>Bartonella elizabethae</i>	(? fleas)	small mammal
15		<i>Bartonella florenceae</i>	unknown	small mammal
16		<i>Bartonella fuyuanensis</i>	unknown	small mammal
17	Cat scratch disease (1X)	<i>Bartonella grahamii</i>	(? fleas)	small mammal
18		<i>Bartonella heixiaensi</i>	unknown	small mammal
19	Cat scratch disease, other	<i>Bartonella henselae</i>	(flea, ticks), cat attack	
20		<i>Bartonella jaculi</i>	unknown	small mammal
21		<i>Bartonella japonica</i>	(lice (<i>Hoploplura affinis</i>))	small mammal
22	Endocarditis	<i>Bartonella koehlerae</i>	(fleas)	cat
23		<i>Bartonella pachyromydis</i>	unknown	small mammal
24		<i>Bartonella peromysci</i>	(fleas)	small mammal
25		<i>Bartonella queenslandensis</i>	(fleas)	small mammal
26	Endocarditis, Trench fever	<i>Bartonella quintana</i>	body lice	human
27		<i>Bartonella rattaaustraliani</i>	(flea)	small mammal
28	Bacteremia, splenomegaly (1x)	<i>Bartonella rochalimae</i>	sandflies	dogs (humans)
29???	Breitschwerdt	<i>Bartonella schoenbuchensis</i>	(Deer keds, biting flies, ticks)	wild ruminant
30		<i>Bartonella senegalensis</i>	(? tick <i>Ornithodoros sonrai</i>)	?? None
31		<i>Bartonella silvatica</i>	unkown	small mammal
32		<i>Bartonella talpae</i>	(? fleas)	small mammal
33		<i>Bartonella taylorii</i>	(? fleas)	small mammal
34	Febrile illness	<i>Bartonella tribocorum</i>	(fleas)	small mammal
35	Bacteremia	<i>Bartonella vinsonii</i> subsp. <i>arpensis</i>	(fleas, ticks)	small mammal
Endocarditis		<i>Bartonella vinsonii</i> subsp. <i>berkhoffii</i>	ticks	dog
		<i>Bartonella vinsonii</i> subsp. <i>vinsonii</i>	(ear mites)	small mammal

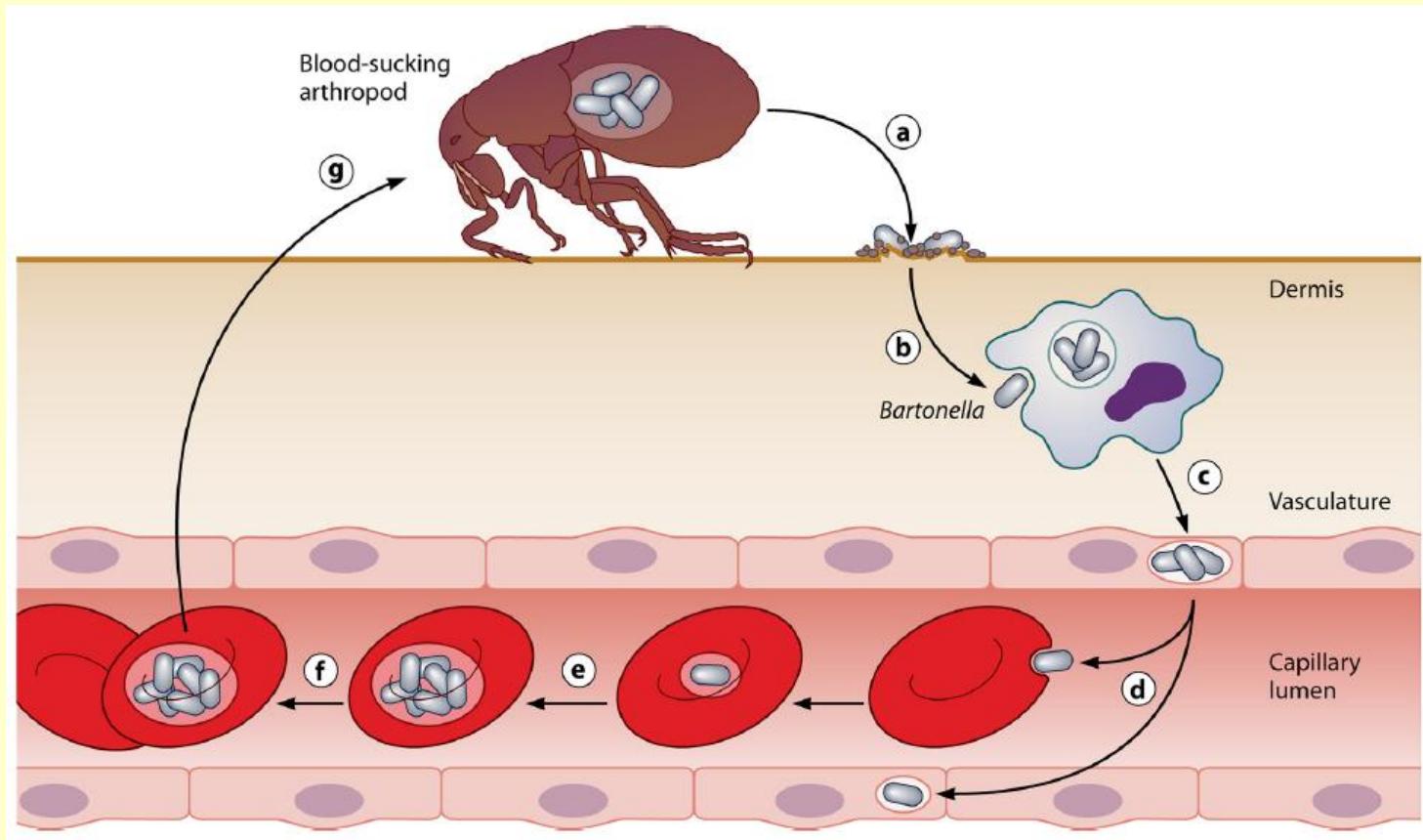
Number of Bartonella hosts



Zoonotic potential of *Bartonella* species

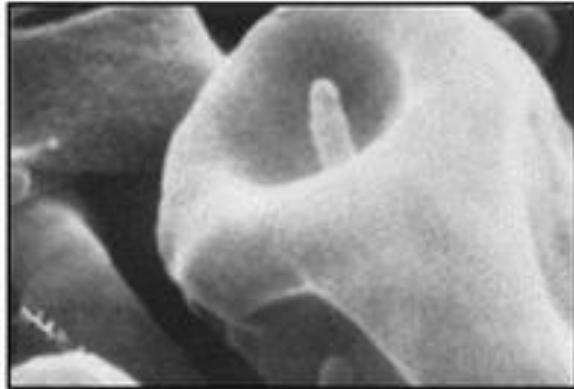


Bartonellae & infection strategy

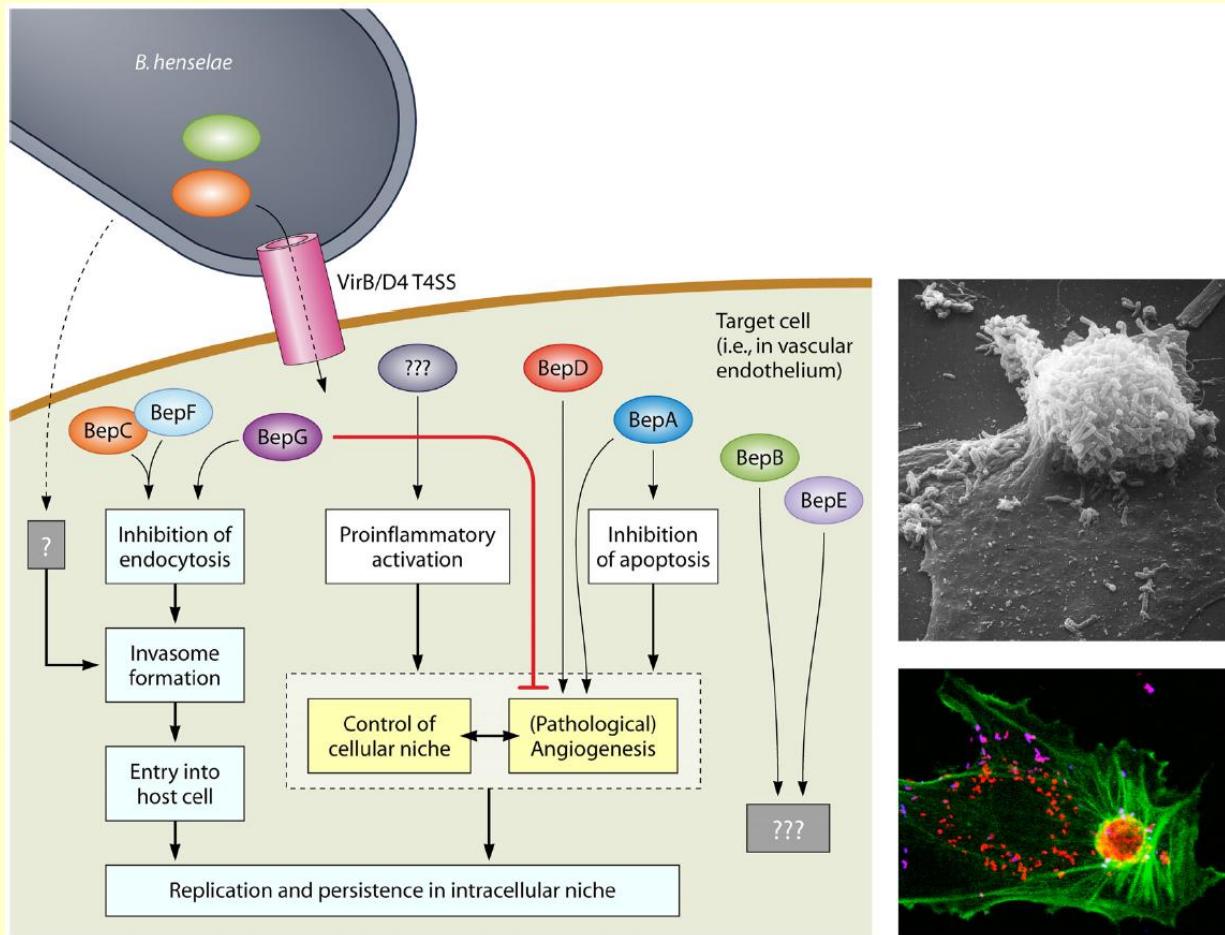


- **Immunocompetent patients** – milder diseases, cat scratch disease, urban trench fever etc.
- **Immunocompromised patients** – endocarditis, angioproliferative lesions, osteomyelitis and various body organ can be affected

Scanning electron micrographs of deformin-induced invaginations and pits on erythrocyte membranes



Bartonella posses secretion system IV

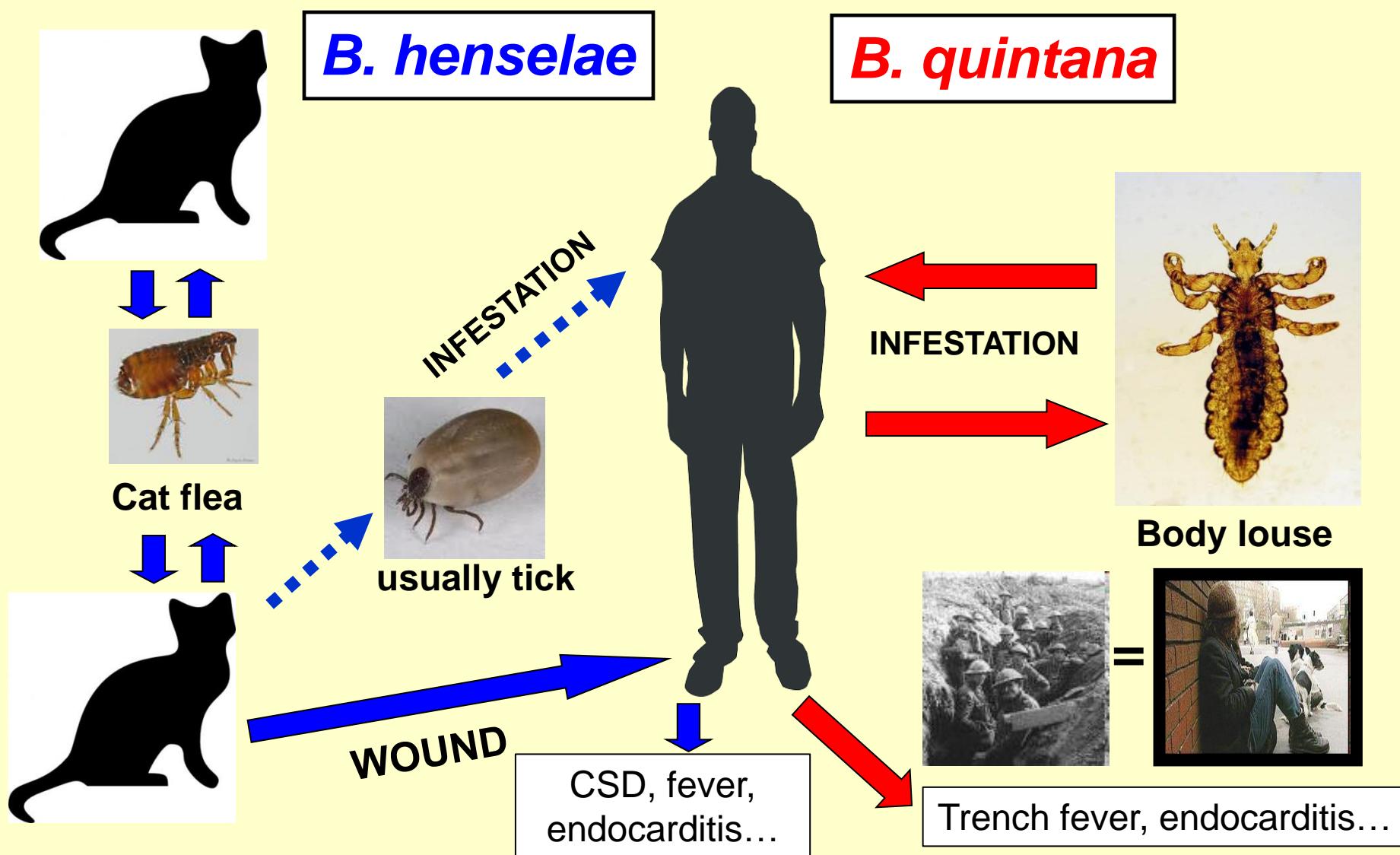


VirB/D4 T4SS and Beps of *B. henselae*. Left, the different virulence phenotypes of the VirB/D4 T4SS and the Beps are summarized in a schematic drawing. It becomes apparent that the diverse cellular activities converge toward the establishment, maintenance, and control of an intracellular niche. Right, the formation of an invasome on human endothelial cells infected with *B. henselae* is shown as visualized by different techniques (top, scanning electron microscopy; bottom, confocal microscopy and immunocytochemistry). In the bottom part intracellular bacteria appear red, extracellular bacteria appear purple, and the actin cytoskeleton is stained green. Note the remarkable actin ring structure forming around the bacterial aggregate (Harms, Dehio, CMR, 2012).

Most significant agent of infections

- Prior to 1990 only *B. bacilliformis*: endemic - Andes, reservoir – human, vector – sandfly **Lutzomyia** (*Brenner, Journal of Clinical Microbiology, 1991*)
- Most frequent „modern“ bartonellae & infection
B. henselae, reservoir – cat
B. quintana, reservoir – human (*Anderson, Clinical Microbiology Reviews, 1997*)

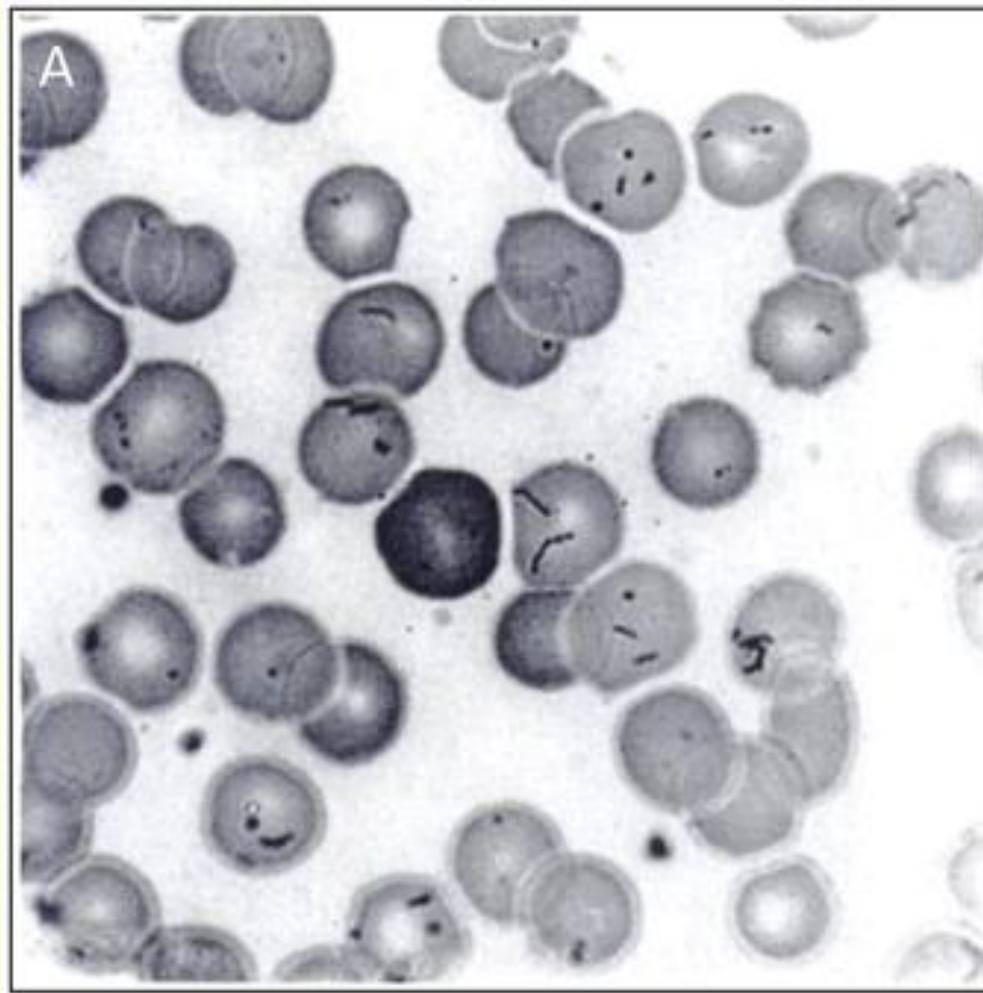
Infectious cycle of *B. henselae*, *B. quintana*



Felinosis and systemic infections

<i>B. henselae</i>	<ul style="list-style-type: none">• Felinosis (cat scratch disease)• Bacteremia and endocarditis• Bacillary angiomatosis, peliosis• Osteomyelitis• Glomerulonephritis
<i>B. quintana</i>	<ul style="list-style-type: none">• Endocarditis and bacteremia• Urban trech fever• Bacillary angiomatosis, peliosis

Clinical manifestations of Carrión's disease.

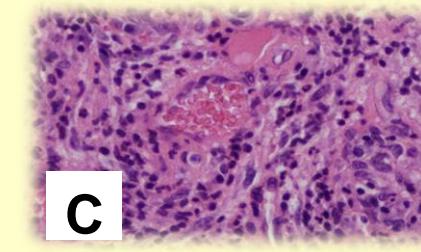
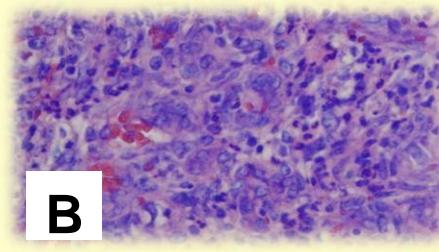
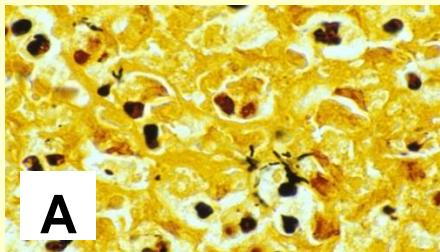


B. quintana & bacillary angiomatosis

- Female patient (43 year old), kidney transplant complication because of immunosupresion
- 4 weeks after - tumorous nodules appeared



Bacillary
angiomes

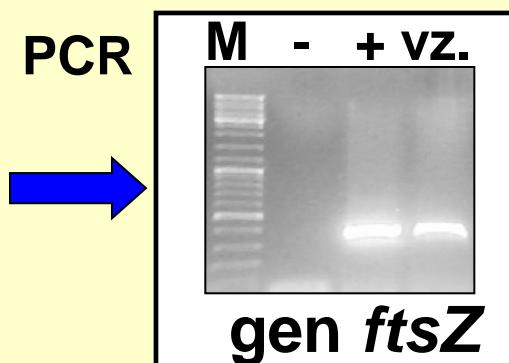


Histology

- A) Silver staining
- B) Giemsa staining
- C) Hematoxylin-eosin

Biopsy

PCR



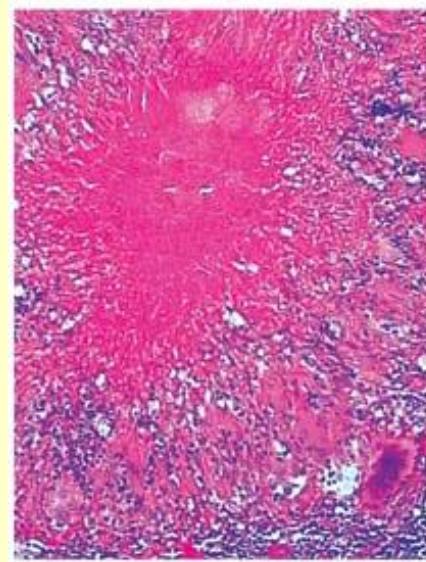
Dg: *B. quintana*
infection

B. henselae - symptoms & pathology of infections

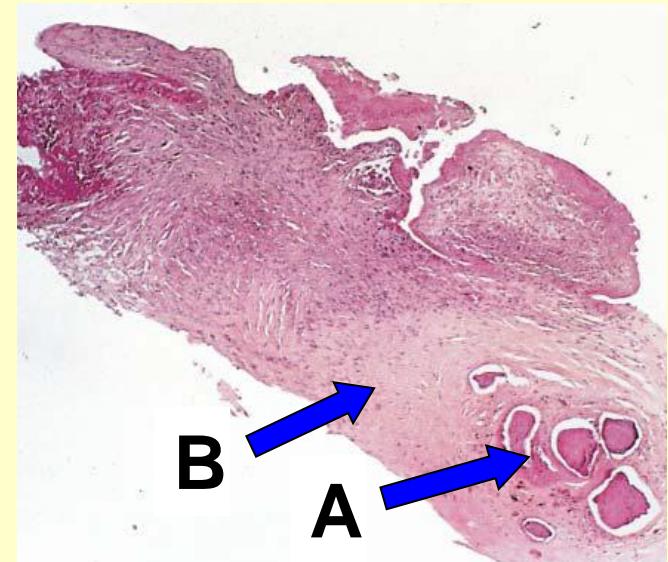


**Felinosis
axillary
lymphadenitis**

*Fitzpatrick's Dermatology
in General Medicine,
7th edition, 2007*



**Felinosis
necrotic
lymphadenitis**
Hematoxylin-eosin
*Manfredi et al.
Braz. J. Inf. Dis., 2006*

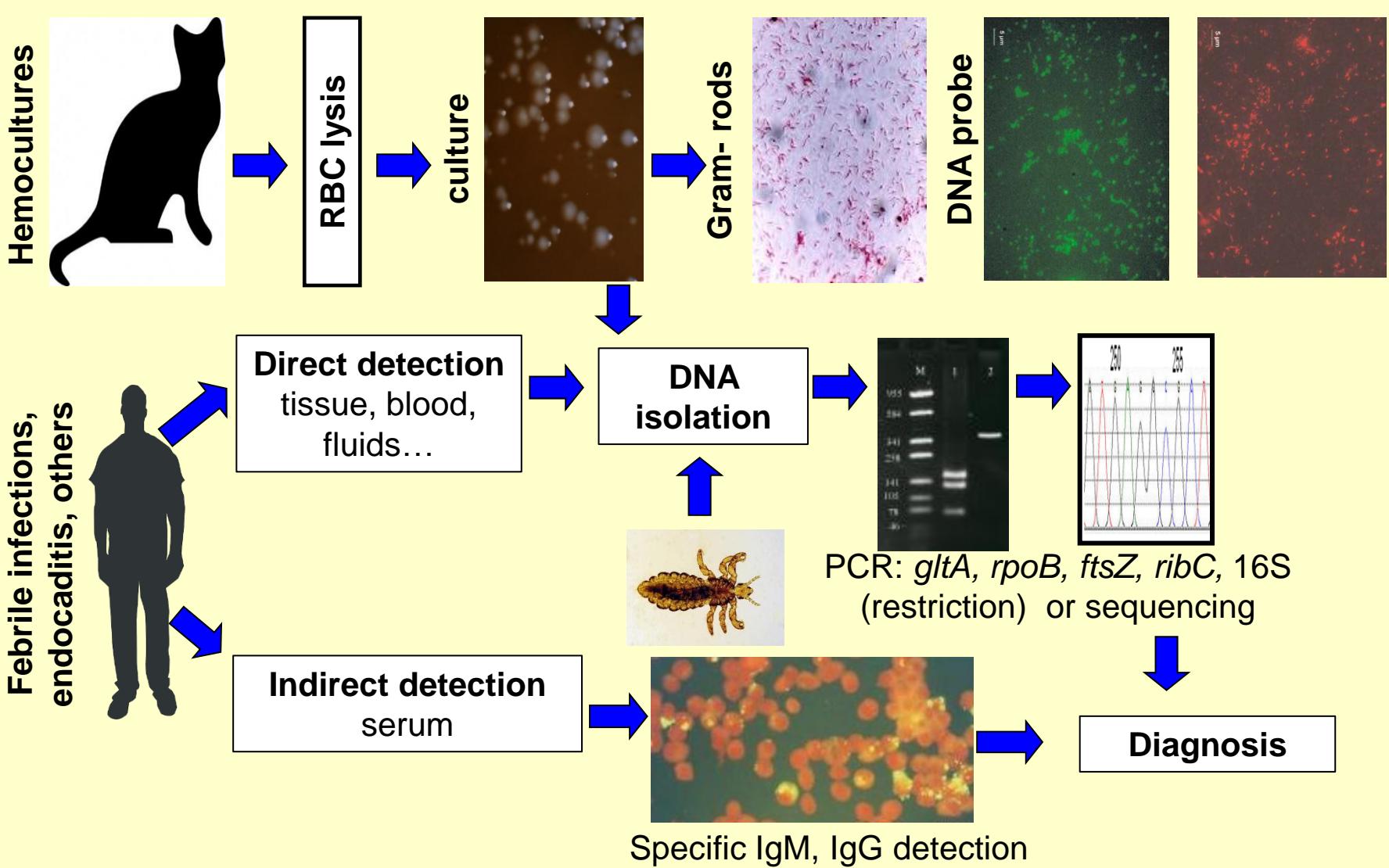


**Endocarditis, heart
valve**

**A. calcification
B. fibrotisation**

Hematoxylin modification
*Lepidi et al., Am. J. Clin. Pathol.,
2000*

Bartonellae detection in hosts, vectors & patients (e.g. *B. henselae*, *B. quintana*)



Thanks for your attention !