



2,434 cases of Q fever

From the French National reference center
1991-2016

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IHU Méditerranée Infection

Q fever

Coxiella burnetii, gram negative intracellular bacteria

Worldwide zoonosis (excepted in New Zealand)

Endemic: French Guiana, Netherlands, Africa, France

Acute Q fever (hepatitis and pneumonia) and **persistent *C. burnetii* infection** (cardio-vascular infection)

Persistent *C. burnetii* infection: a changing paradigm

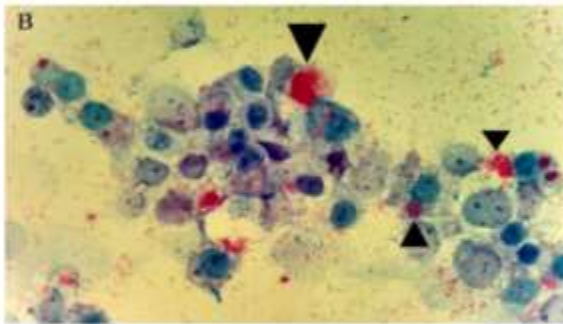
Organic lesion

+ Microbiological evidence (serology, PCR, culture)



Phase I: 100, IgM, 0, IgA 0

Phase II: 200, IgM, 0, IgA, 0



Peacock, *Infect Imm*, 1983

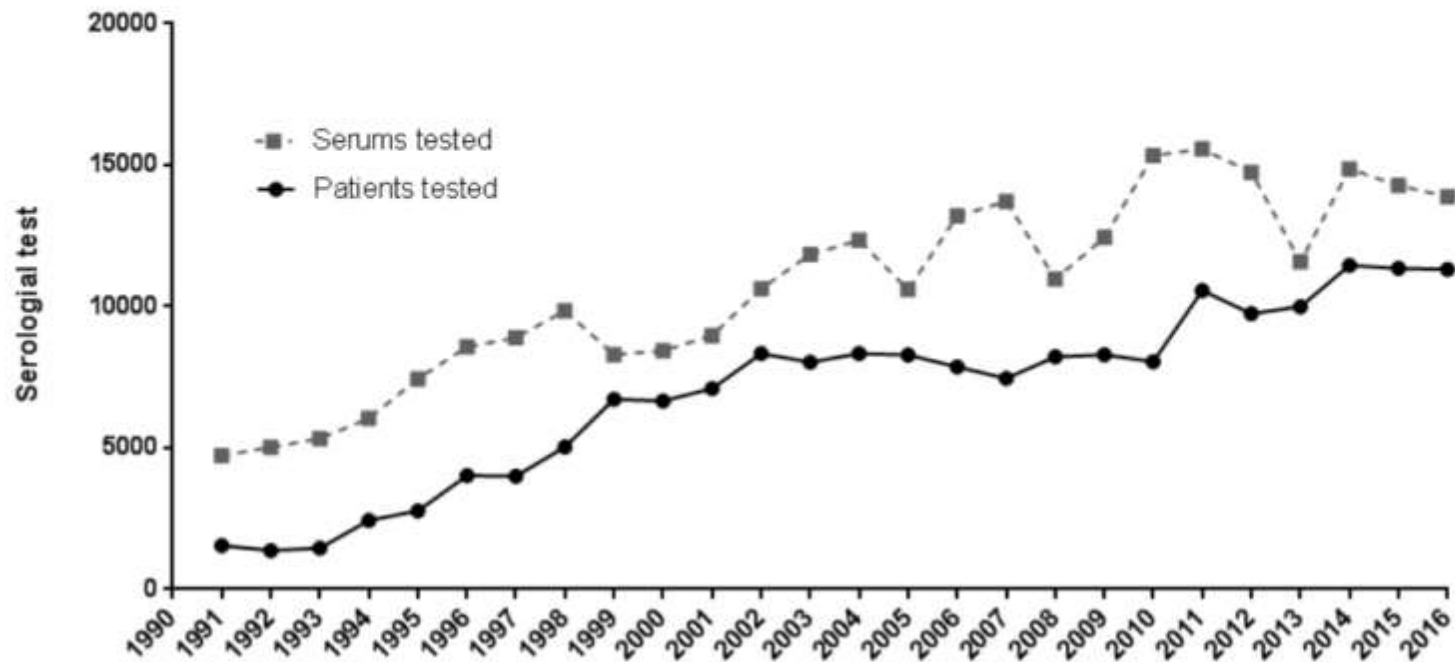
Raoult, *Clin infect Dis*, 2017

Melenotte, *Int J infect dis*, 2018

National reference Center for Q fever Marseille

Serological test performed each year in the French National Reference Center of *Coxiella burnetii* infection.

Serological tests for Q fever each year in the French NRC



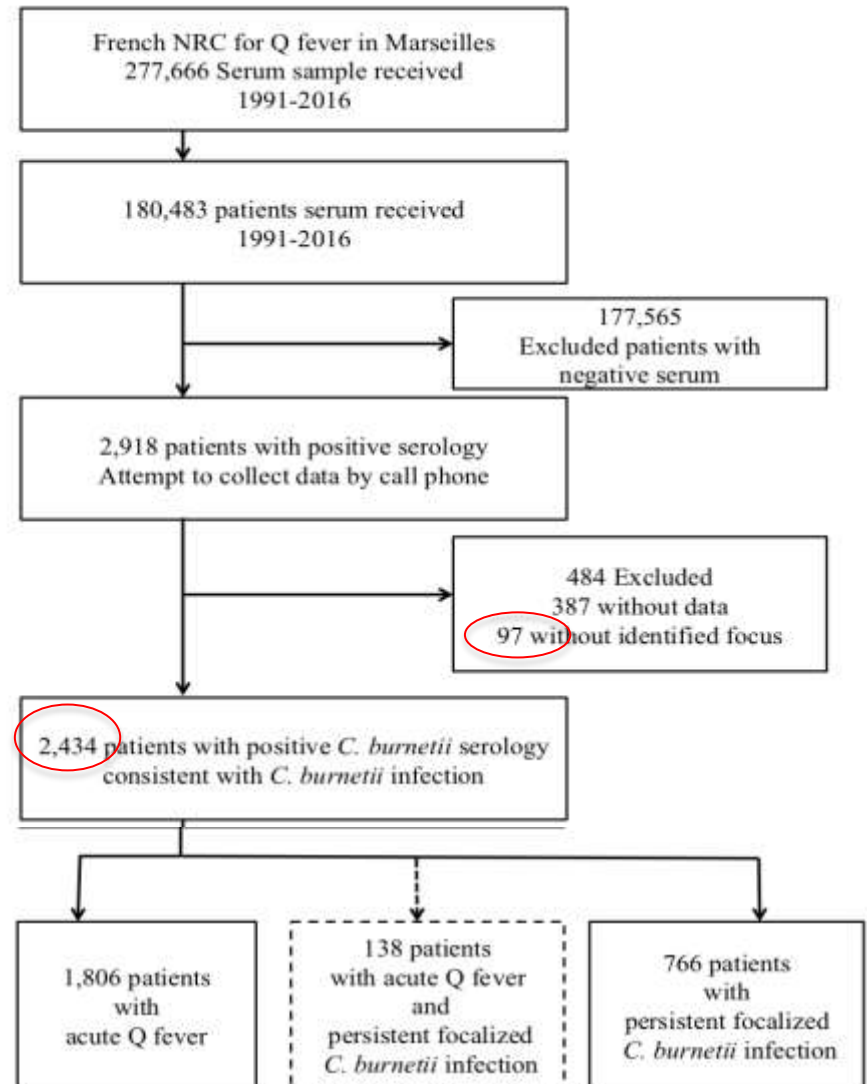
Patients included

Primary (acute) *C. burnetii* infection

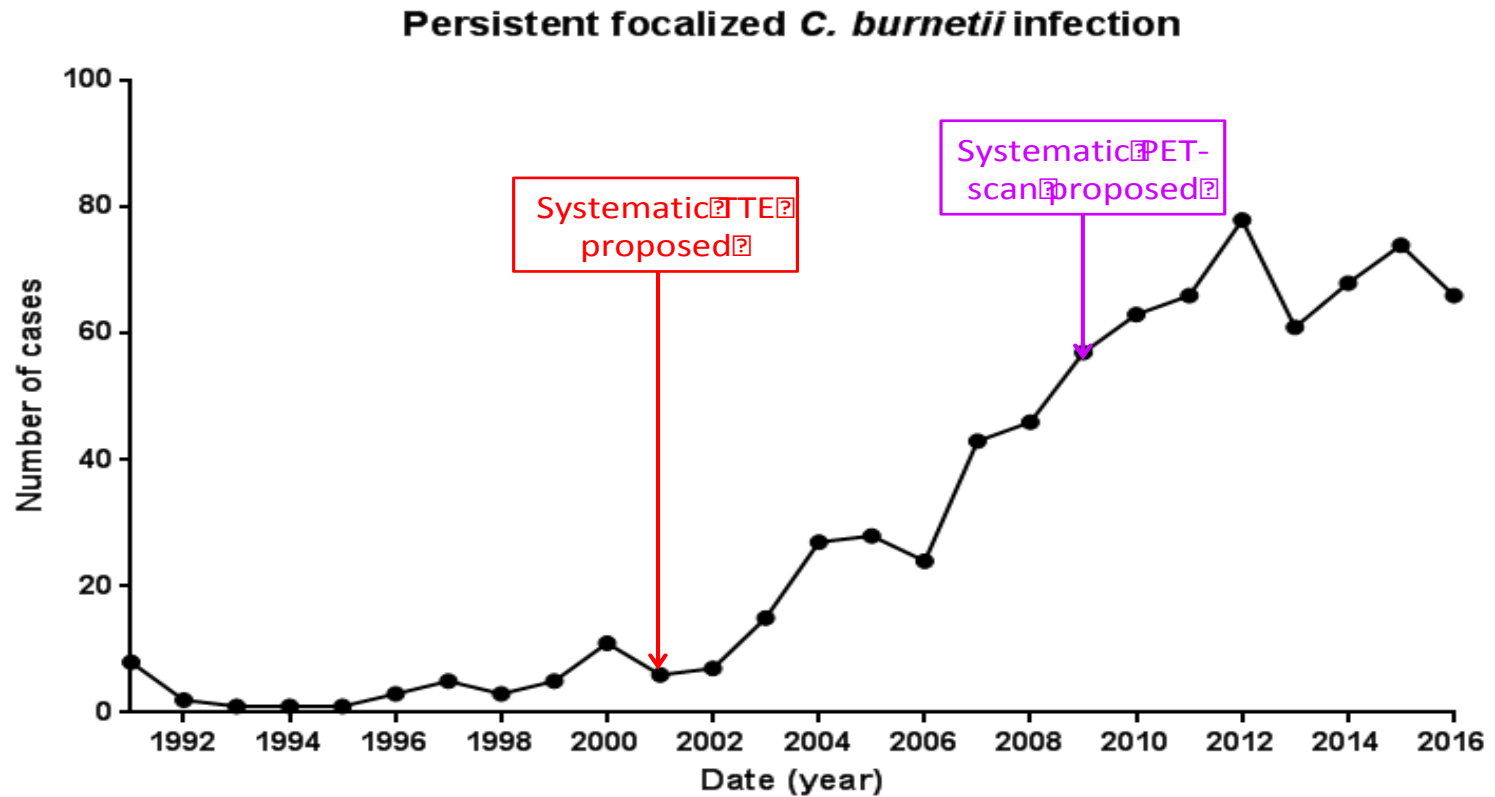
- acute clinical symptoms
- IgG titers II \geq 200 and IgM II \geq 50
- or seroconversion within three months of the primary symptoms.

Persistent *C. burnetii* focal infection

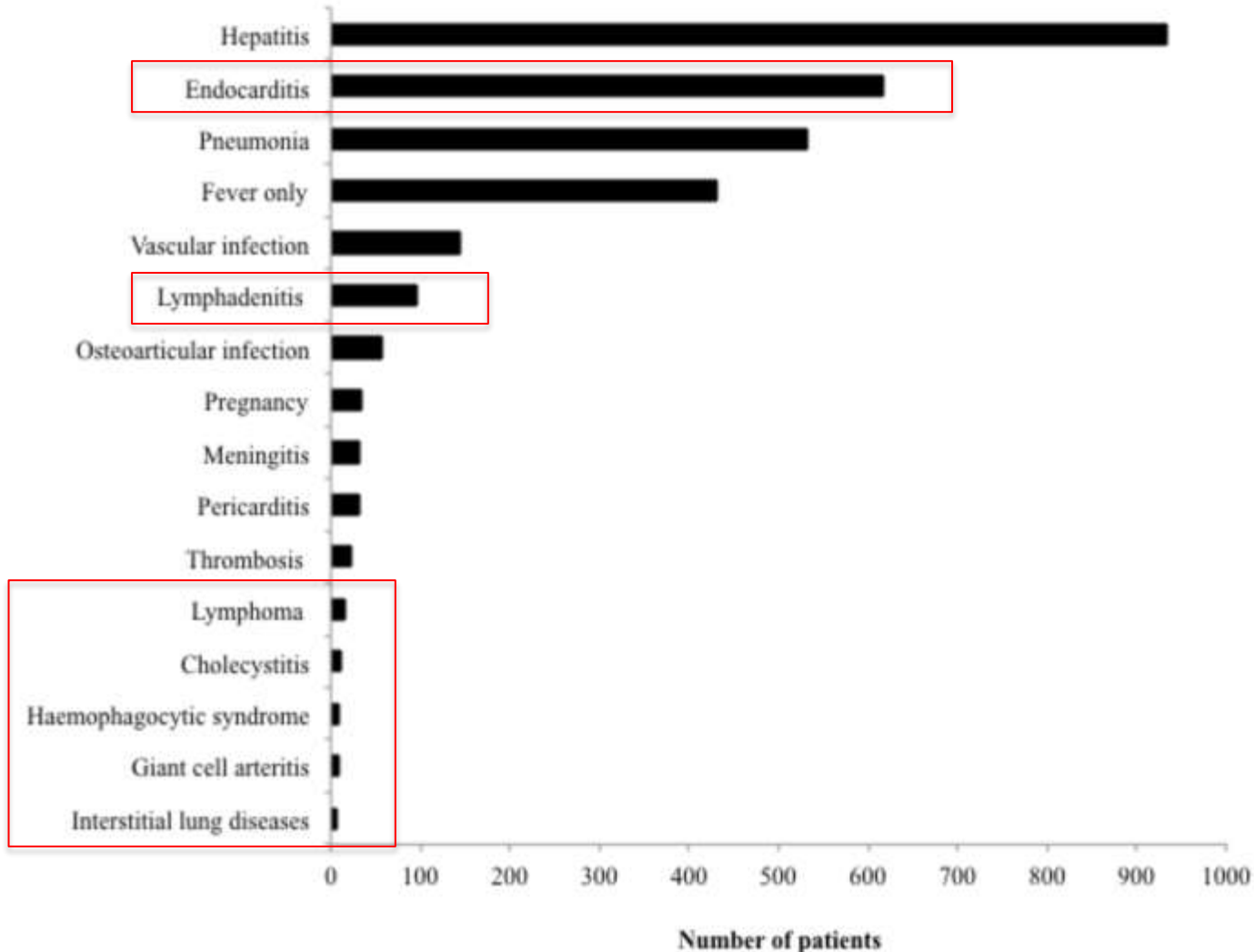
- Persistence of clinical symptoms >3 months
- Identification of an infectious focus



C. burnetii persistent infection



Q fever clinical presentation



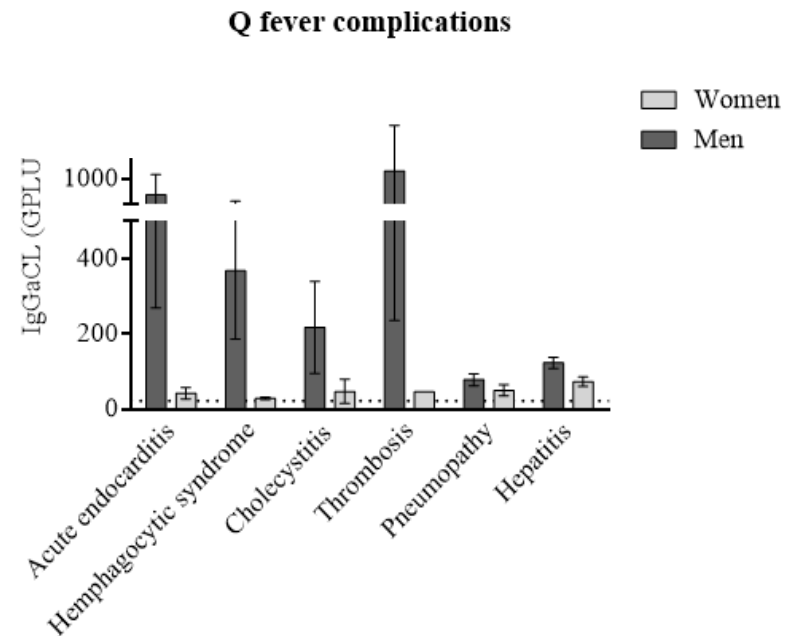
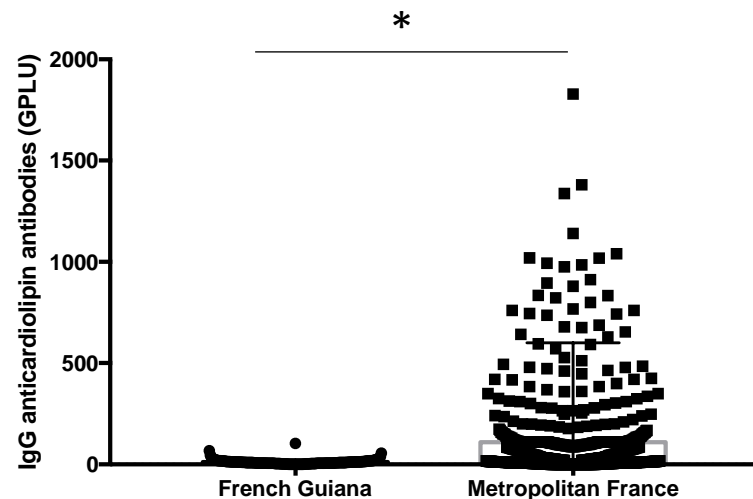
Acute Q fever

Acute Q fever complication and anticardiolipins

eTable 13. ROC analysis of IgG anticardiolipin antibodies and acute Q fever complications

| Variable | AUC | 95%CI | | P |
|----------------------------|-----|-------|-----|-------|
| Acute Q fever endocarditis | .67 | .58 | .76 | .0001 |
| Hemophagocytic syndrome | .78 | .67 | .89 | .003 |
| Meningitis | .68 | .56 | .79 | .01 |
| Thrombosis | .72 | .6 | .85 | .002 |
| Alithiasic cholecystitis | .75 | .6 | .9 | .05 |

AUC: area under curve, CI: confidence interval



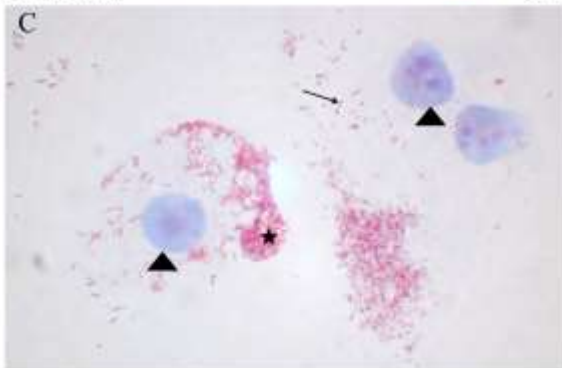
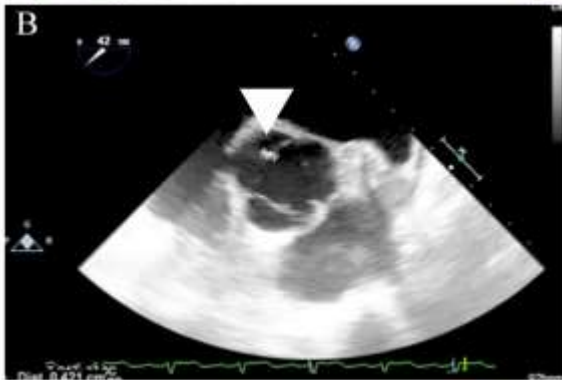
Acute Q fever endocarditis

50 cases of acute Q fever endocarditis

28 % had a preexisting valvulopathy

70% had positive IgG aCL (>22GPLU)
OR=2.4; 95 confidence interval [1.2-4.9]; p=0.011

3 positive culture from blood



Persistent *C. burnetii* complications

C. burnetii persistent infection

Clinical presentation of persistent *C. burnetii* infections: 766 patients

| | Endocarditis N=581 | | Vascular infection N=145 | | Osteo articular infection N=56 | |
|--------------------------|-----------------------|-------|-----------------------------|-------|-----------------------------------|-------|
| Age (mean±SD) | 59.4±17.3 | - | 63.4±14.3 | - | 59.6±19.9 | - |
| Sex (men) | 419 | 72.1% | 127 | 88.2% | 37 | 66.1% |
| Immunosuppression | 22 | 3.8% | 6 | 4.2% | 1 | 1.8% |
| Valvular predisposition | 449 | 77.4% | 57 | 39.6% | 7 | 12.5% |
| Prosthetic material | 204 | 35% | 62 | 44% | 10 | 17.8% |
| Endocarditis | - | - | 49 | 34.0% | 7 | 12.5% |
| Vascular infection | 49 | 8.4% | - | - | 11 | 19.2% |
| Osteoarticular infection | 8 | 1.3% | 11 | 7.5% | - | - |
| Hepatitis | 123 | 21.2% | 28 | 19.4% | 6 | 10.7% |
| Pneumonia | 52 | 8.9% | 10 | 6.9% | 2 | 3.6% |
| Lymphadenitis | 26 | 4.5% | 6 | 4.2% | 4 | 7.1% |
| Acute endocarditis | 13 | 2.2% | 1 | 0.7% | 0 | 0% |
| Lymphoma | 10 | 1.7% | 2 | 1.4% | 0 | 0% |
| Meningitis | 7 | 1.2% | 0 | 0% | 1 | 1.8% |
| Hemophagocytic syndrome | 1 | 0.2% | 1 | 0.7% | 0 | 0% |

Q fever the hidden pathogen of interstitial lung diseases

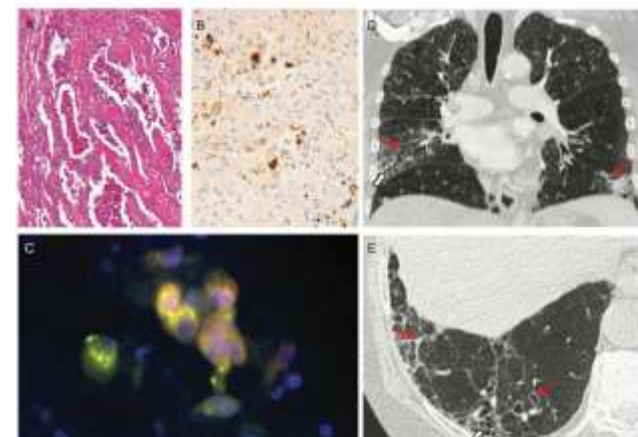
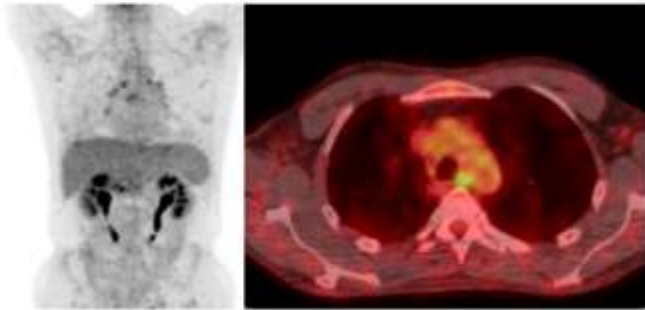


Table 1. Clinical Description of Patients With Q Fever and ILD

| Patient Sex/Age, y | Geographic Origin | Medical History | Positive Autoimmune Test Result | Immunosuppressive Treatment | <i>C. burnetii</i> Focus Infection (in Addition to Lung) | <i>C. burnetii</i> Serology: IgG1, IgM1, IgA1 IgG11, IgM11, IgA11 Levels | <i>C. burnetii</i> Microbiological Analysis | Delay Between Q Fever and ILD, mo ^a | Radiological Feature | ILD <i>C. burnetii</i> Infection | Hospitalization | Q Fever Treatment | Outcome |
|------------------------|------------------------|--|---------------------------------|-----------------------------|--|--|---|--|----------------------|----------------------------------|-----------------|-------------------|--|
| 1/M/72 (index patient) | Troyes, France | Asbestos exposure | ANCAs (MPO) | Corticoid and rituximab | Endocarditis (A1B3C2) | 800, 0, 0, 400, 0, 0 | IHC, FISH, and PCR ^c | -60 ^b | Unclassified | Definite | ICU | HD | Partial clinical improvement at 7.1 mo |
| 2/M/51 | Reunion Island, France | Rheumatoid polyarthritis | RF/ANAs | Corticoids | Endocarditis (A0B1C2) | 400, 0, 100, 800, 0, 200 | No | -1 ^b | Unclassified | Possible | ICU | No | Died at 0.2 mo |
| 3/F/70 | Marseille, France | Tobacco | No | No | NI | 800, 0, 0, 800, 0, 0 | No | -24 ^b | UIP | Possible | Medicine | No | Partial clinical improvement at 51 mo |
| 4/M/57 | French Guiana | Dermatopolymyositis | No | Corticoid and methotrexate | Endocarditis (A2B2C0) | 51 200, 0, 3200, 102 400, 0, 6400 | No | 21 | Unclassified | Possible | Medicine | HD | Partial clinical improvement at 51 mo |
| 5/M/78 | French Guiana | Asbestos exposure, amiodarone use, tobacco use | No | No | NI | 400, 0, 0, 400, 0, 0 | No | 0.5 | Unclassified | Possible | Medicine | D | Partial clinical improvement at 2 mo |
| 6/M/83 | Toulouse, France | Amiodarone use | No | No | NI | 1600, 0, 0, 0, 0, 0 | No | 0.5 | Unclassified | Possible | ICU | HD | Partial clinical improvement at 4 mo |
| 7/F/59 | Marseille, France | Tobacco use | ANCAs | Azathioprine | Granulomatous hepatitis | 3200, 0, 100, 1600, 0, 200 | iF ^d | 0 | NSIP | Possible | ICU | HD | Partial clinical improvement at 7.1 mo |

Lymphadenitis

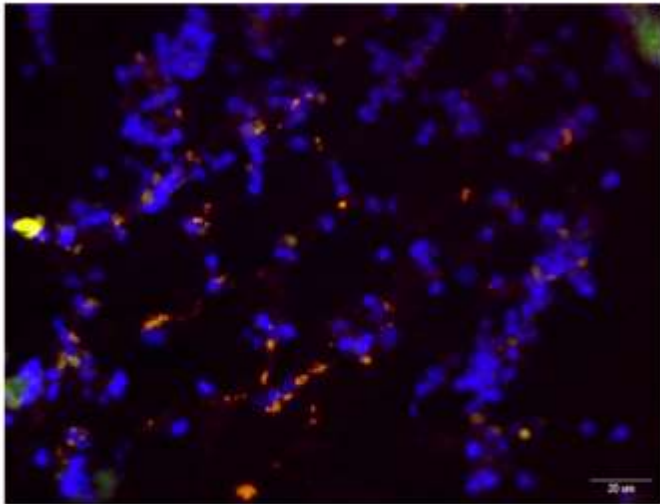
Focalized persistent *C. burnetii* lymphadenitis as the unique focus of *C. burnetii* persistent infection. Identification of the deep and persistent infective focus with PET-scan.



97 lymphadenitis

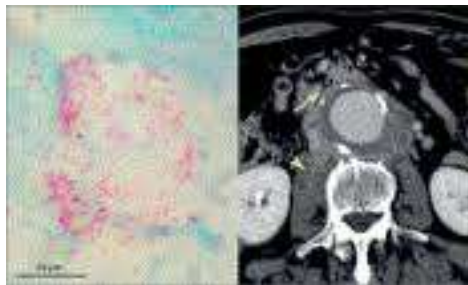
44% isolated with PET-scanner

associated with a **risk of lymphoma**
HR=77.4, 95% CI [21.2-281.8], $p < .001$



Biopsy revealed positive FISH targeting the specific *C. burnetii* 16S rRNA
A & B. PET scan with positive mediastinal lymphadenitis
C. Positive FISH targeting *C. burnetii* 16S rRNA

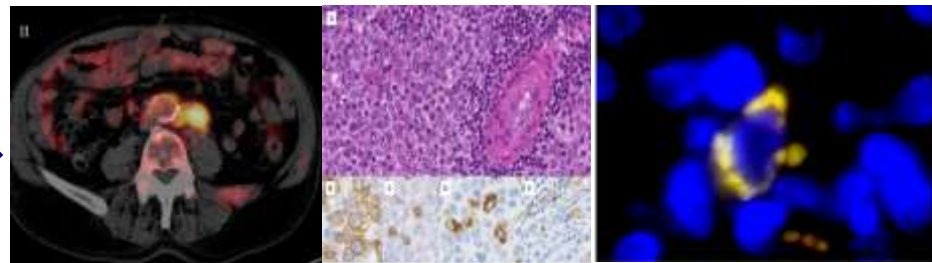
Q fever and lymphoma



C. burnetii vascular infection

Melenotte, *Lancet*, 2012

18
months



Follicular lymphoma

C. burnetii in the tumoral microenvironment

Melenotte, *Blood*, 2016

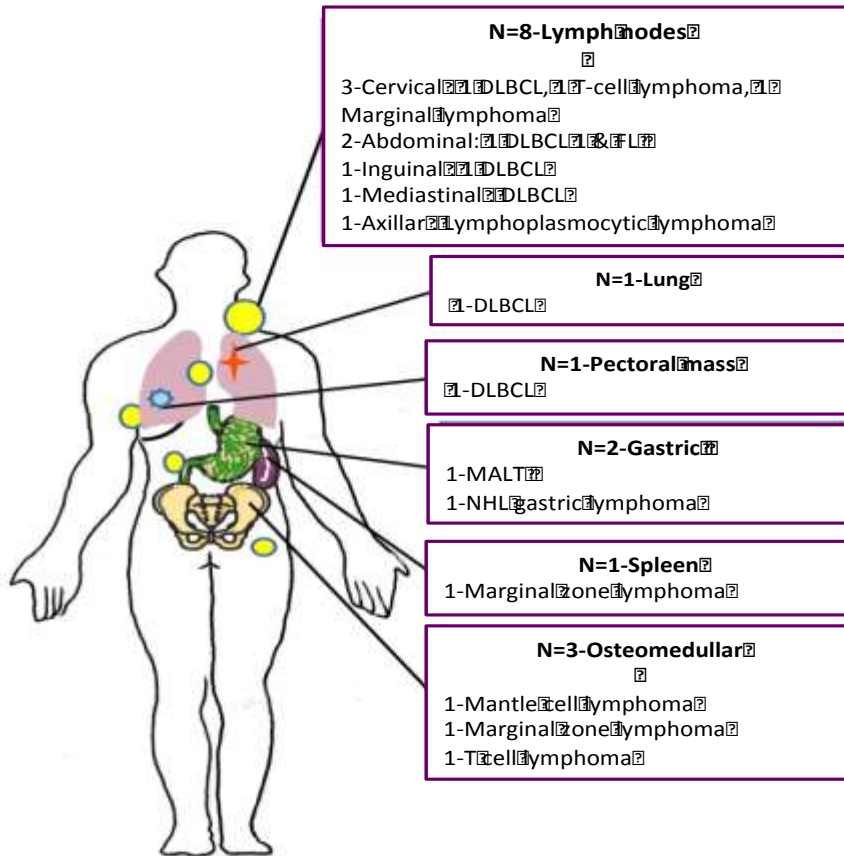
Patients with Q fever had a **25-fold increased risk of NHL**

C. burnetii identified in **macrophages** and **plasmacytoid dendritic cells**

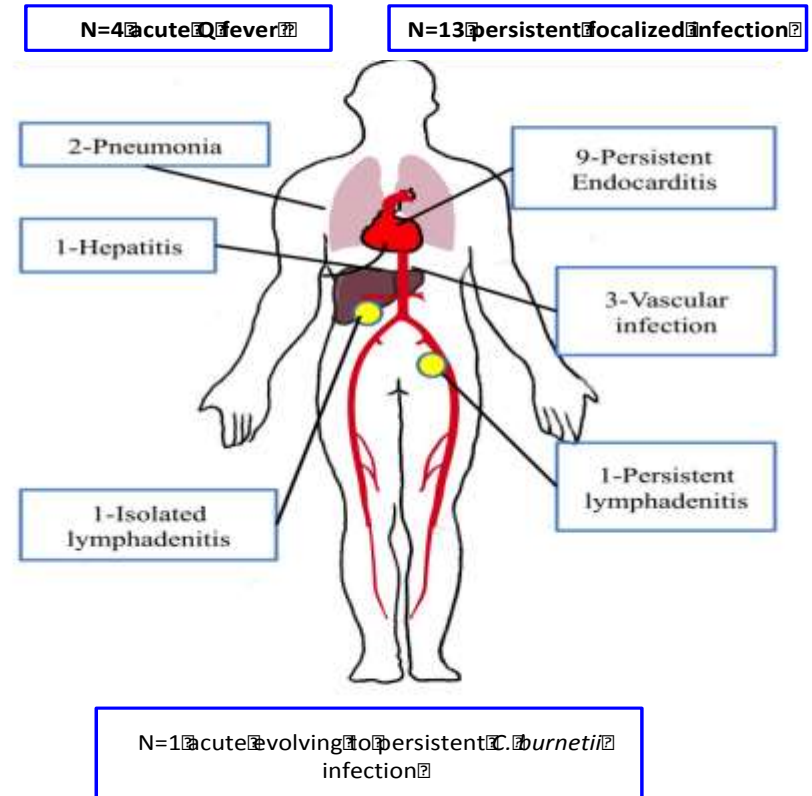
Gradient IL-10 in patients with persistent *C. burnetii* infection, lymphadenitis and lymphoma

Q fever and lymphoma

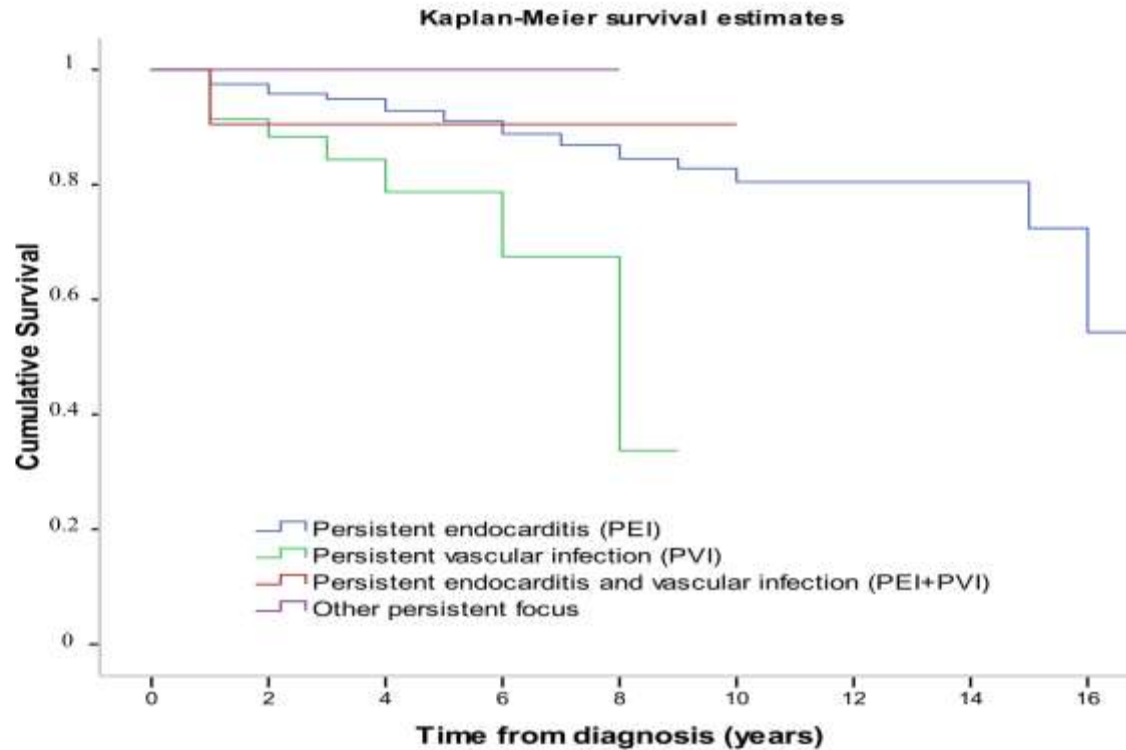
Anatomical site of lymphoma



Coxiella burnetii infectious foci



Mortality rate



| | Number at risk | | | | | | | | |
|------------------------|----------------|-----|-----|-----|----|----|----|----|---|
| Endocarditis | 533 | 245 | 157 | 105 | 63 | 35 | 22 | 16 | 8 |
| Vascular infection | 96 | 24 | 12 | 6 | 2 | 0 | 0 | 0 | 0 |
| Both (PEI and PVI) | 49 | 18 | 9 | 5 | 2 | 2 | 0 | 0 | 0 |
| Other persistent focus | 87 | 18 | 9 | 2 | 1 | 0 | 0 | 0 | 0 |

Limitations

¼ patients with acute Q fever were lost follow-up

C. burnetii cardio-vascular infections were probably over-represented

Conversely, the mortality rate might be underestimated because of potential loss to follow-up.

Conclusion

Cardio-vascular : fatal complication

Anticardiolipin antibodies associated with acute complications

Neglected rare foci

Alithiasic cholecystitis

Haemophagocytic syndrome

Acute Q fever endocarditis

Lymphadenitis

Lymphoma

Interstitial lung disease

Use TTE and PET !

Thank you

Marseille

Didier Raoult

Camélia Protopopescu

Patrizia Carrieri

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Jean-Louis Mège

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You

