

2nd International Crypto-conference, Dublin Ireland



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What are crypto-infections?

- Cryptic (crypto) Infections are infection caused by as yet unidentified pathogens which serves as the direct target of the immune response
- Crypto-infections, which include tick-borne bacterial pathogens and others, are well recognised as a significant burden of disease in both human and animal hosts. However, much remains to be done to further diagnose, understand the underlying pathogenesis, and optimally treat these infections.

One health initiative (1)

- The One Health Initiative is a movement to forge co-equal, all inclusive collaborations between physicians, osteopathic physicians, veterinarians, dentists, nurses, and other scientific-health and environmentally related disciplines, including the American Medical Association, American Veterinary Medical Association, American Academy of Pediatrics, American Nurses Association, American Association of Public Health Physicians, the American Society of Tropical Medicine and Hygiene, the Centers for Disease Control and Prevention (CDC), the United States Department of Agriculture (USDA), and the U.S. National Environmental Health Association (NEHA). Additionally, more than 979 prominent scientists, physicians, and veterinarians worldwide have endorsed the initiative.

Irish Tick Study

Location	% Positive	CI 95%	<i>Borrelia</i> species
Killarney (Kerry)	2%	(0% - 6%)	<i>B. valaisiana</i>
Kilmacthomas (Waterford)	6%	(0% - 13%)	<i>B.b s.l</i>
Kilmacthomas (Survey 2)	4%	(0% - 9%)	1x <i>B. garinii</i> strain T25 1x <i>B. garinii</i> strain BgVir
Portumna (Galway-South)	12%	(3% - 21%)	<i>B.b s.l</i>
Portumna (Survey 2)	6%	(0% - 13%)	1x <i>B. miyamotoi</i> 2x <i>B. garinii</i> strain BgVir
Glendalough (Wicklow)	2%	(0% - 6%)	<i>B. valaisiana</i>
Glenveagh (Donegal)	6%	(0% - 13%)	1x <i>B. garinii</i> strain BgVir 2x <i>B. garinii</i> strain Bernie
Clifden (Galway-West)	2%	(0% - 6%)	<i>B.b s.l</i>
Total	5%	(3% - 7%)	
<i>B. garinii</i>	70%	(7/10)	
<i>B. miyamotoi</i>	5%	(1/10)	
<i>B. valaisiana</i>	10%	(2/10)	

B.b s.l = *Borrelia burgdorferi sensu lato*

CI 95% = 95% Confidence Interval

Lambert JS, Cook MJ, Healy JE, Murtagh R, Avramovic G, Lee SH. Metagenomic 16S rRNA gene sequencing survey of *Borrelia* species in Irish samples of *Ixodes ricinus* ticks. *PLoS One*. 2019; 1–11. Available:

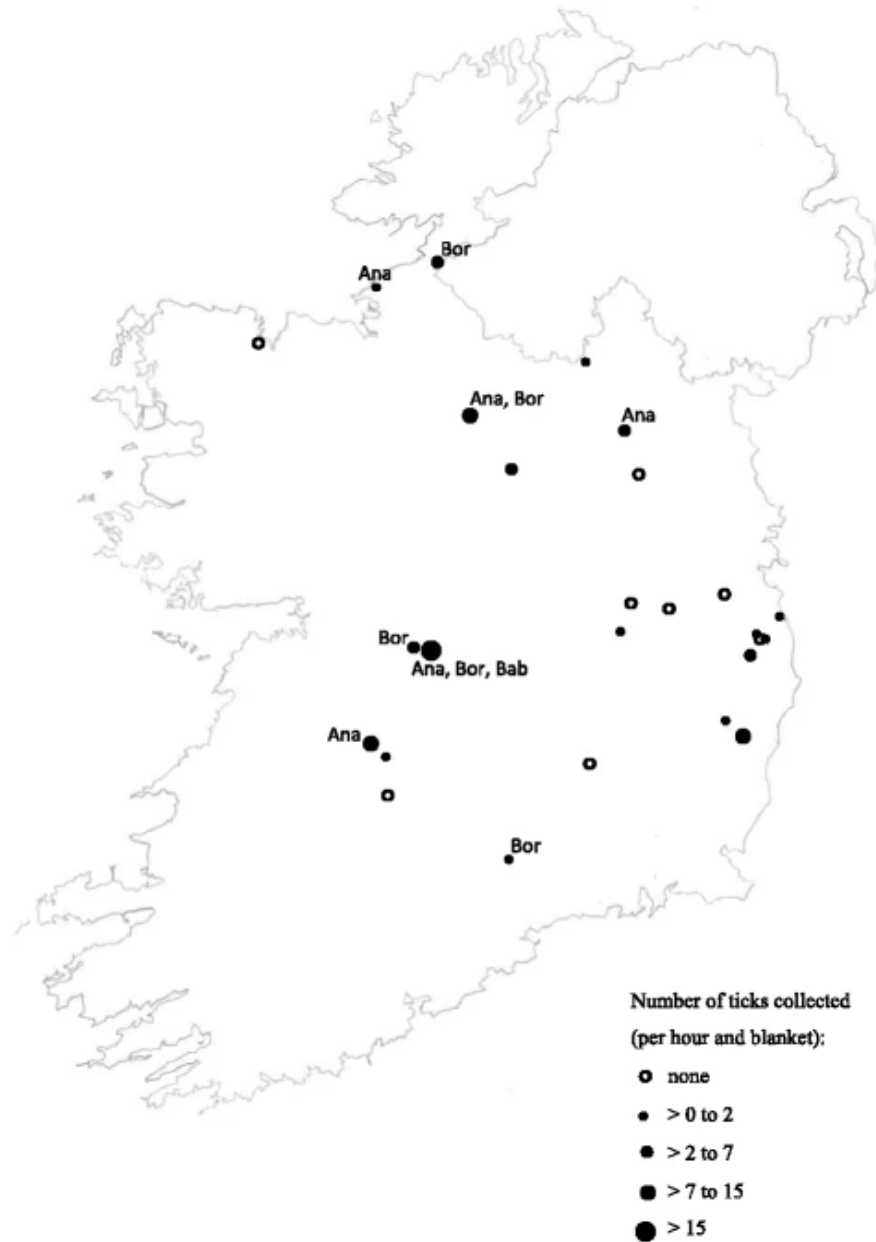
<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0209881>



Fig 1. Sampling locations in Ireland for *Ixodes ricinus* ticks in May & June 2018.

UCD Veterinary studies

- Evidence of TBD found in tick populations in Ireland^[17] Borrelia, Anaplasma, Babesia
- Irish patients are not routinely tested for co-infections



Tick-borne Pathogens

- Borreliosis: *Borrelia burgdorferi* (multiple species and strains) also *B. americana*, *B. andersonii*, *B. bissettii*, *B. carolinensis*, *B. afzelii*, *B. garinii*, *B. spielmanii*, *B. lonestari*, *B. bissetti*, *B. kurtenbachii*, *B. chilensis*, *B. lusitaniae*, *B. valaisiana*, *B. sinica*, *B. bavariensis*, *B. finlandensis*, *B. japonica*, *B. miyamotoi*, *B. Yangtze*, *B. tanukii*, *B. turdi*
- Babesiosis: *Babesia microti*, *Babesia duncani*, etc.
- Other Piroplasm Diseases: Theileria and Cytauxzoon
- Ehrlichiosis: *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and *Ehrlichia ewingii*.
- Human Monocytic Ehrlichiosis: *Ehrlichia chaffeensis*
- Rocky Mountain Spotted Fever: *Rickettsia rickettsii*
- Tick-borne Relapsing Fever: *Borrelia turicatae*, *B. hermsi*
- Tularemia: *Francisella tularensis*
- Q Fever: *coxiella burnetii*
- Tick Paralysis (Tick Toxicosis): Unknown
- Powassan/Deer Tick Virus Encephalitis: Powassan and deer tick viruses
- Colorado Tick Fever: Colorado tick fever virus
- Southern Tick-Associated Rash Illness (STARI) or Master's Disease
- Bartonellosis: *Bartonella species*
- Mycoplasmosis: *Mycoplasma species*
- Tick-borne Encephalitis: *Flavivirus*
- Maculatum Disease: *Rickettsia parkeri*
- Relapsing Fever: *Borrelia hermsii*
- *Rickettsia philipii*
- Bourbon virus
- *Toxoplasma gondii*
- Who knows what else?

An Audit of 100 patients from an Infectious Disease Practice, Dublin, Ireland, with Lyme-associated symptoms

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Sophie Westley² & John S Lambert^{1,2}

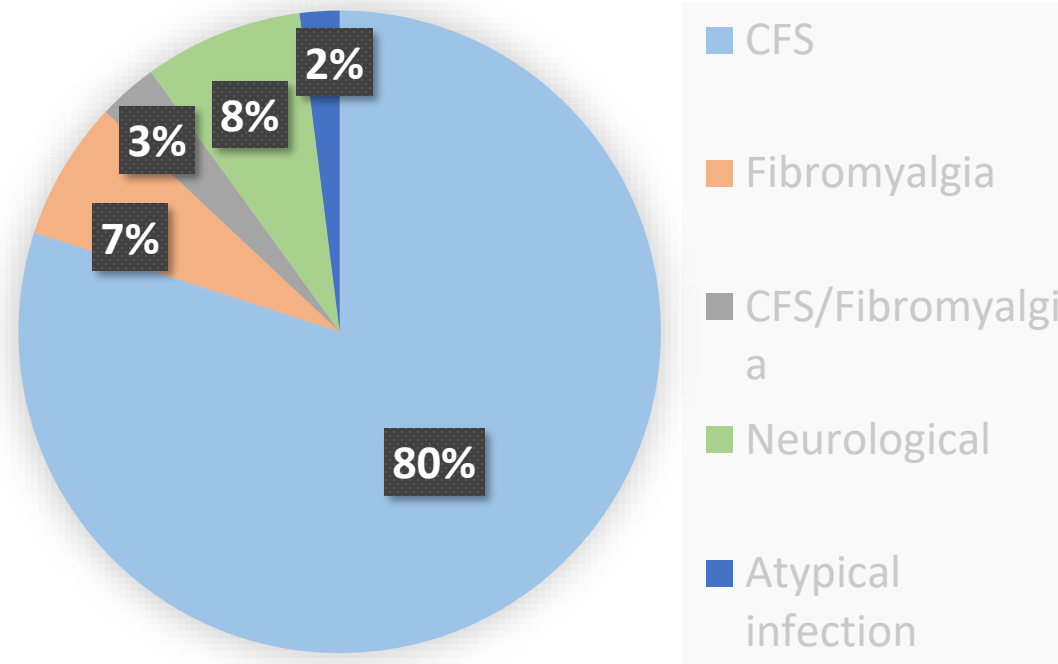
*Mater Misericordiae University Hospital Dublin, Ireland, ¹University College
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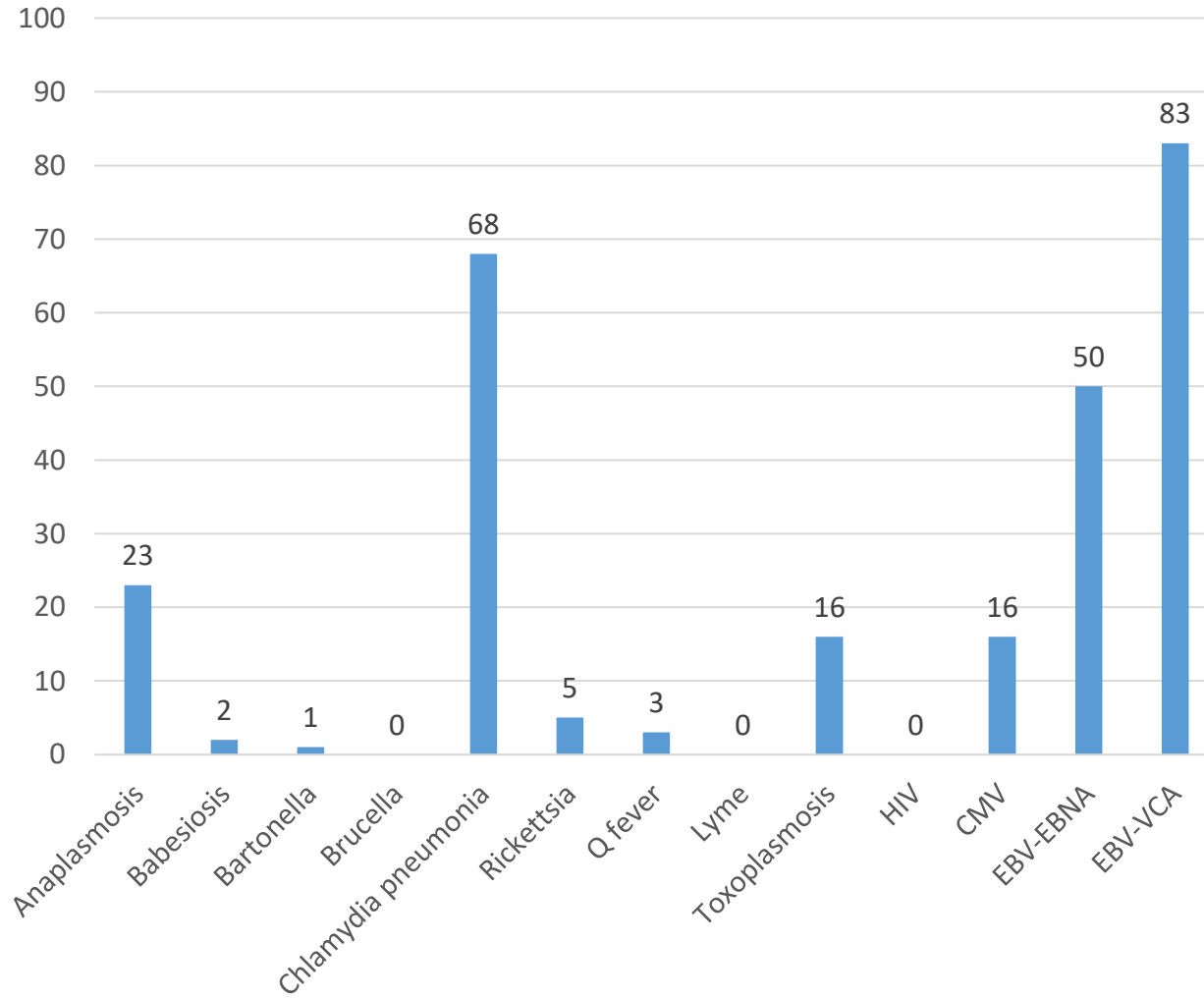


Methods & Results

Diagnosis at presentation



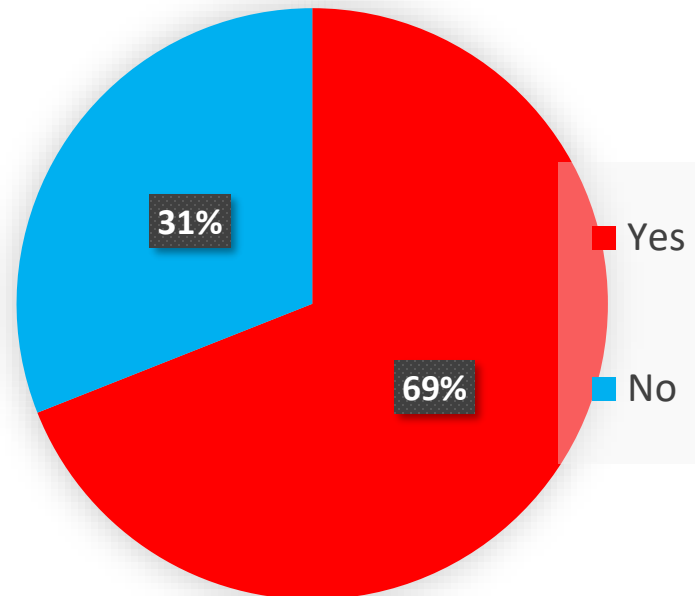
Infectious agents identified by antibody testing



Treatment response

- Treatment results are available on 71% of patients that returned after 6 months of treatment for review, of whom:
 - 69% responded
 - 31% did not respond

Treatment response of patients that returned to clinic



Research Priorities

Dr. JANEY CRINGEAN, TRUSTEE, Professor Jack Lambert



Registered Scottish charity (SCIO): SC049151

www.lymeresourcecentre.com

Research Priorities

1. Identify all tick-borne infections in Scotland
2. Identify the true burden of infection and illness from tick-borne infections in humans and animals in Scotland
3. Understand the impact of polymicrobial co-infections on human health
4. Research optimal treatment for persistent infections
5. Research optimal non-pharmaceutical interventions that support recovery

Priority 3 Understand the impact of polymicrobial co-infections on human health

- Many patients appear to be infected with multiple pathogens. How does that impact disease severity and influence treatment required?
- Surveying the patients, from patient groups who have 'chronic lyme', would enable patient engagement and allow correlation of symptoms with identified infections.
- Current surveillance in the UK and Ireland does not accurately represent the 'burden of disease' from tickborne infections.
- Ireland has less than 20 cases reported annually (CNS/spinal fluid required for reporting, the government generously report 200 cases, calculations from burden of disease estimate 2500 annually)

Priority 4: Research optimal treatment for persistent infections

- **Persistent infection** is now accepted by scientists working at the cutting edge of Lyme disease research – how should it be treated?
- Persistent symptoms have been seen in humans with late diagnosis and treatment
 - **Diagnosis and Treatment of Lyme Arthritis**
Arvikar SL, Steere AC. Infect Dis Clin N Am 29 (2015) 269–280. <https://www.ncbi.nlm.nih.gov/pubmed/25999223>
“A minority of patients may have persistent synovitis for months or several years after oral and intravenous antibiotic therapy”.
- Persistent infection shown in many animal studies
 - **Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to *Borrelia burgdorferi* by tick feeding**
Embers ME, Hasenkampf NR, Jacobs MB, et al. PLoS One. 2017 Dec 13;12(12):e0189071. <https://www.ncbi.nlm.nih.gov/pubmed/29236732>
When treatment of rhesus macaques was delayed by 16 weeks after the bite, recommended doses of doxycycline for 28 days did not eradicate the disseminated infection, demonstrated by the presence of persistent, intact, metabolically-active *B. burgdorferi*.

Priority 4: Research optimal treatment for persistent infections

- Now increasing **evidence for persistent infection in humans**
 - **Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis**
Oksi J, Marjamäki M, Nikoskelainen J, Viljanen MK. Ann Med. 1999 Jun;31(3):225-32. <https://www.ncbi.nlm.nih.gov/pubmed/10442678>
“treatment of Lyme borreliosis with appropriate antibiotics for even more than 3 months may not always eradicate the spirochete”
 - **Isolation of live Borrelia burgdorferi sensu lato spirochaetes from patients with undefined disorders and symptoms not typical for Lyme borreliosis**
Rudenko N, Golovchenko M, Vancova M, et al. Clin Microbiol Infect. 2016 Mar;22(3):267.e9-15. <https://www.ncbi.nlm.nih.gov/pubmed/26673735>
 - **Persistent Borrelia Infection in Patients with Ongoing Symptoms of Lyme Disease**
Middelveen MJ, Sapi E, Burke J, et al. Healthcare (Basel), 2018 Apr 14;6(2). <https://www.ncbi.nlm.nih.gov/pubmed/29662016>
*“Using multiple corroborative detection methods, we showed that patients with persistent Lyme disease symptoms may have **ongoing spirochetal infection despite antibiotic treatment**, similar to findings in non-human primates”*
 - **The Long-Term Persistence of Borrelia burgdorferi Antigens and DNA in the Tissues of a Patient with Lyme Disease**
Sapi E, Kasliwala RS, Ismail H, et al. Antibiotics (Basel), 2019 Oct 11;8(4). <https://www.ncbi.nlm.nih.gov/pubmed/31614557>
Borrelia was found in **four different organs** in human autopsy tissues from a well-documented patient who was antibody positive before treatment, **antibody negative, CSF positive, and culture positive after standard treatment**, who clinically **improved with longer course antibiotics** which was safe and efficacious, but who ultimately **died when treatment was withdrawn**.
- Eminent Stanford University research scientists have made a video
 - <https://youtu.be/0a3sBmleRQo> - *“I think now we are past the denial stage”*

Priority 4: Research optimal treatment for persistent infections

- A re-review of the world literature on treatment of Lyme and co-infections
- Design of new studies on treating such infections
- Taking into consideration
 - that more than one infection may be contributing to patient illness
 - novel antibiotics and combinations of standard antibiotic treatment for persister forms and biofilm-like colonies
 - treatment based on 'response to treatment', as is done for all other infectious diseases
 - support for the immune support, including use of Low Dose Naltrexone
 - methods of reducing inflammation

Wish you were here in Dublin: contact gavramovic@mater.ie for any culinary requests



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