
# Interactive discussion on difficult cases

# The challenge of Lyme disease

**Dr Sandra Pearson**
**Medical Director, Lyme Disease Action**

# Lyme Disease Action

- Registered charity founded by a group of scientists in 2003
  100% funded by voluntary contributions
- Serving patients, clinicians and researchers
- Striving for the prevention and treatment of Lyme disease and associated tick borne diseases.

http://www.lymediseaseaction.org.uk/

https://www.facebook.com/pages/Lyme-Disease-Action/122058224483868

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# Personal details

- Medical Director of Lyme Disease Action since 2010. Academic and consultancy role
  sandra.pearson@lymediseaseaaction.org.uk
- Lived experience: Husband developed Lyme neuroborreliosis in 2008. Registered Carer until 2011
- Consultant Psychiatrist: CPD includes Lyme disease
- LDA CPD: International Conferences: Lyme and TBDs
- Member of ESCMID: European Society for Microbiology & Infectious Diseases
- Social media: Twitter @PearsLDA

# LDA: Position and Assumptions

- Lyme disease/TBDs are an increasing public health concern. Importance of medical/public awareness and primary/secondary prevention #BeTickAware
- No gold standard test. No reliable biomarker/test of cure. Current serology tests have limitations.
- Importance and challenge of clinical diagnosis
- Need UK guidance
- Genuine uncertainties in diagnosis/treatment
- Need UK-based research
- Better care and treatment

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# Lyme disease: Uncertainties

James Lind Alliance
Priority Setting Partnerships

http://www.jla.nihr.ac.uk/

Home | About the JLA | The PSPs | Top 10s | JLA Guidebook | News and Publications | Maki

You are in: Home » The PSPs » Lyme disease » Top 10 priorities

## Lyme Disease Top 10

1. How effective are the current UK tests in detecting infections due to the genospecies and strains of B burgdorferi sl in the UK and which single test and what combination of tests performs best in diagnosing or ruling out active Lyme disease. Should stage of the disease and patient age be taken into account when interpreting these tests?
2. What key questions (clinical and epidemiological) should be considered to help make a diagnosis of Lyme disease in children and adults in the UK and would a weighting table be useful?
3. What is the best treatment for children and adults presenting with a) early Lyme disease without neurological involvement and not including erythema migrans and b) late Lyme disease of any manifestation? To include consideration of drug(s), dose, duration.
4. What is the optimal course of action if symptoms relapse after a treatment course is finished?

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# ECDC Scientific Advice

Leeflang *et al. BMC Infectious Diseases* (2016) 16:140
DOI 10.1186/s12879-016-1468-4

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

## The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis

M. M. G. Leeflang[12*], C. W. Ang[1], J. Berkhout[2], H. A. Bijlmer[3], W. Van Bortel[4], A. H. Brandenburg[5], N. D. Van Burgel[6], A. P. Van Dam[7], R. B. Dessau[8], V. Fingerle[9], J. W. R. Hovius[10], B. Jaulhac[11], B. Meijer[13], W. Van Pelt[3], J. F. P. Schellekens[13], R. Spijker[14], F. F. Stelma[15], G. Stanek[16], F. Verduyn-Lunel[17], H. Zeller[4] and H. Sprong[3]

**Background:** Interpretation of serological assays in Lyme borreliosis requires an understanding of the clinical indications and the limitations of the currently available tests.
We therefore systematically reviewed the accuracy of serological tests for the diagnosis of Lyme borreliosis in Europe.

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

**Methods:** Searched EMBASE and MEDLINE and contacted experts.

Studies evaluating the diagnostic accuracy of serological assays for Lyme borreliosis in Europe were eligible.

Study selection and data-extraction were done by two authors independently.

Assessed study quality using the QUADAS-2 checklist.

Used a hierarchical summary ROC meta-regression method for the meta-analyses.

Potential sources of heterogeneity were test-type, commercial or in-house, Ig-type, antigen type and study quality.

These were added as covariates to the model, to assess their effect on test accuracy.

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**Results:** 78 studies evaluating an ELISA or immunoblot against a reference standard of clinical criteria were included.

None of the studies had low risk of bias for all QUADAS-2 domains.

Sensitivity was highly heterogeneous:

- Erythema migrans 50% (40 - 61%)
- Neuroborreliosis 77% (67 - 85 %)
- Acrodermatitis chronica atrophicans 97 % (94 - 99%)
- Unspecified Lyme borreliosis 73% (53 - 87%)

Specificity was around 95% in studies with healthy controls, but around 80% in cross-sectional studies.

Two-tiered algorithms or antibody indices did not outperform single test approaches.

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RESEARCH ARTICLE

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studies.

**Conclusions:**

- The observed heterogeneity and risk of bias complicate the extrapolation of our results to clinical practice.
- The usefulness of the serological tests for LD depends on the pre-test probability and subsequent predictive values in the setting where the tests are being used.
- Future diagnostic accuracy studies: Prospectively planned cross-sectional studies, done in settings where the test will be used in practice.

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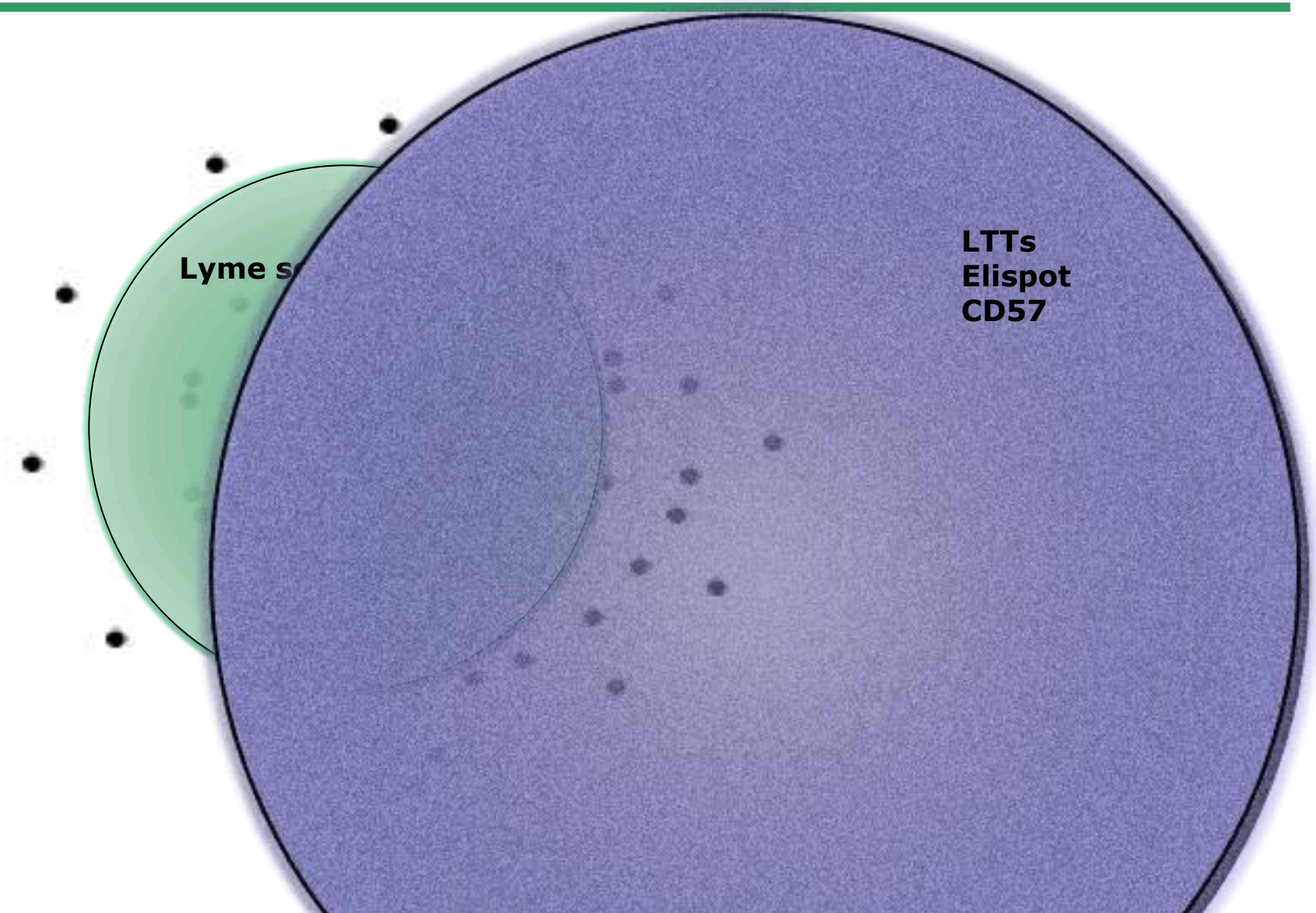
# The problem with over-reliance on serological confirmation



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The case for better care and treatment

**BMC Infectious Diseases**

BioMed Central

Research article

Open Access

# Diagnostic challenges of early Lyme disease: Lessons from a community case series

John Aucott*[1], Candis Morrison[†2], Beatriz Munoz[†3], Peter C Rowe[†4], Alison Schwarzwalder[†2] and Sheila K West[†3]

**Background**

Lyme disease, the most common vector-borne infection in North America, is increasingly reported. When the characteristic rash, erythema migrans, is not recognized and treated, delayed manifestations of disseminated infection may occur.

The accuracy of diagnosis and treatment of early Lyme disease in the community is unknown.

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# The case for better care and treatment

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## Diagnostic challenges of early Lyme disease: Lessons from a community case series

John Aucott*[1], Candis Morrison[2], Beatriz Munoz[3], Peter G Rowe[4]
Ali

**Methods**

A retrospective, consecutive case series of 165 patients presenting for possible early Lyme disease between August 1, 2002 and August 1, 2007 to a community-based Lyme referral practice in Maryland. All patients had acute symptoms of less than or equal to 12 weeks duration. Patients were categorized according to the CDC criteria and data were collected on presenting history, physical findings, laboratory serology, prior diagnoses and prior treatments.

community is unknown.

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# The case for better care and treatment

**BMC Infectious Diseases**

BioMed Central

Research article

Open Access

**Diagnostic challenges of early Lyme disease: Lessons from a**

**Results**

- The majority (61%) of patients in this case series were diagnosed with early Lyme disease
- Of those not presenting with a rash, 54% had been previously misdiagnosed
- Among those with a rash, the diagnosis of erythema migrans was initially missed in 23% of patients
- Of all patients previously misdiagnosed, 41% had received initial antibiotics likely to be ineffective against Lyme disease

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**Conclusion:**

- In high-risk geographic areas, the diagnosis of Lyme disease remains a challenge
- Failure to recognize erythema migrans or alternatively, viral-like presentations without a rash can lead to missed or delayed diagnosis of Lyme disease, ineffective antibiotic treatment, and the potential for late manifestations

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# The case for better care and treatment

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For misdiagnosed patients or those presenting with a viral-like illness, administration of ineffective antibiotics may produce unintended consequences.

In studies showing suboptimal results with azithromycin, patients were often seronegative after treatment, raising the potential impact of sub-optimal therapy on seroconversion and further complicating reliance on a serology-based diagnosis.

In our series, seronegative patients presenting with a viral-like illness were significantly more likely to have been exposed to antibiotics prior to confirmatory serology than those who tested positive.

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# Pre-Test Probability?

**Background history:** Occupation, outdoor pursuits, medical history, medication

**Tick exposure:** Where do they live, ?Travel history

**Tick bite:** May go unnoticed

**Erythema Migrans rash (EM):** Only 65% notice the rash

**Initial symptoms:** First few weeks and months

**Recent history:** How are they now?

**Lyme serology test results:** ?Tested at RIPL, C6 EIA, Immunoblots, Lyme panel

**Antibiotic treatment:** For Lyme or any other condition ?Early inadequate antibiotics ?Immunosuppressed

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# Case study X
# ?LNB/?Atypical Guillain-Barré

- 50 year old woman, long career as a Police officer, about to retire
- Autumn 2012, Spring 2013: 2 Cycling holidays to Connecticut USA
- No known tick bite or EM rash
- 03/06/13: UK hospital admission, bilateral facial palsy, sensory & motor peripheral neuropathy hands & feet (pain, paraesthesia, loss sensation, loss lower limb reflexes) LP1: 05/06/13 ?results
- 05/06/13 Local Lyme ELISA: Positive, diagnosed LNB by consultant physician. Doxycycline 100mg bd 21 days
- Dramatic improvement in symptoms
- Neurology follow-up a week after discharge

# Case study X
# ?LNB/?Atypical Guillain-Barré

- ‘Confirmatory serology’: Negative immunoblots
- Neurologist diagnoses atypical Guillain-Barré syndrome: ‘Miller-Fisher’ syndrome. Doxycycline stopped after 1 week
- Marked deterioration: unable to drive, difficulties walking due to pain and balance problems, marked weight loss, vomiting, joint pains, insomnia…..
- Patient contacts LDA who check results
- 04/07/13: Serology Positive C6 EIA, immunoblots negative
- 04/07/13 LP2 : CSF IgM +ve OspC (153), IgG negative with one sub-threshold band. Raised protein
- 08/07/13 GP Re-commences doxycycline –> clinical improvement
- 11/07/13: Nerve conduction studies: Normal
- Sep 2013: Neuro OPA: “Not Lyme”. Advised to stop doxycycline. Advised to buy a walking stick. Relapse of symptoms

# Case study X
# ?LNB/?Atypical Guillain-Barré

- 16/10/13: GP repeats serology: C6 positive, IgG Equivocal: VlsE+

- 24/10/13: LP3: Normal protein, no WBCs

- 02/12/13: We had a case discussion  with RIPL

- 10/12/13: OPA Infectious diseases
- Jan 2014: Liaison between LDA/RIPL/ID/GP and local consultant: IV treatment authorised

- 15/01/14: IV ceftriaxone 2g/day, 21 days via OPAT
- 02/02/14: "Big improvement", corroborated by family

- 14/02/14: Relapse of symptoms
- 20/05/14: Second course of IV ceftriaxone -> sustained improvement

- 11/04/15: "Really well". Minimal residual symptoms. Corroborated by GP

# Evidence for re-treatment

A Reappraisal of the US Clinical Trials of Post-Treatment Lyme Disease Syndrome

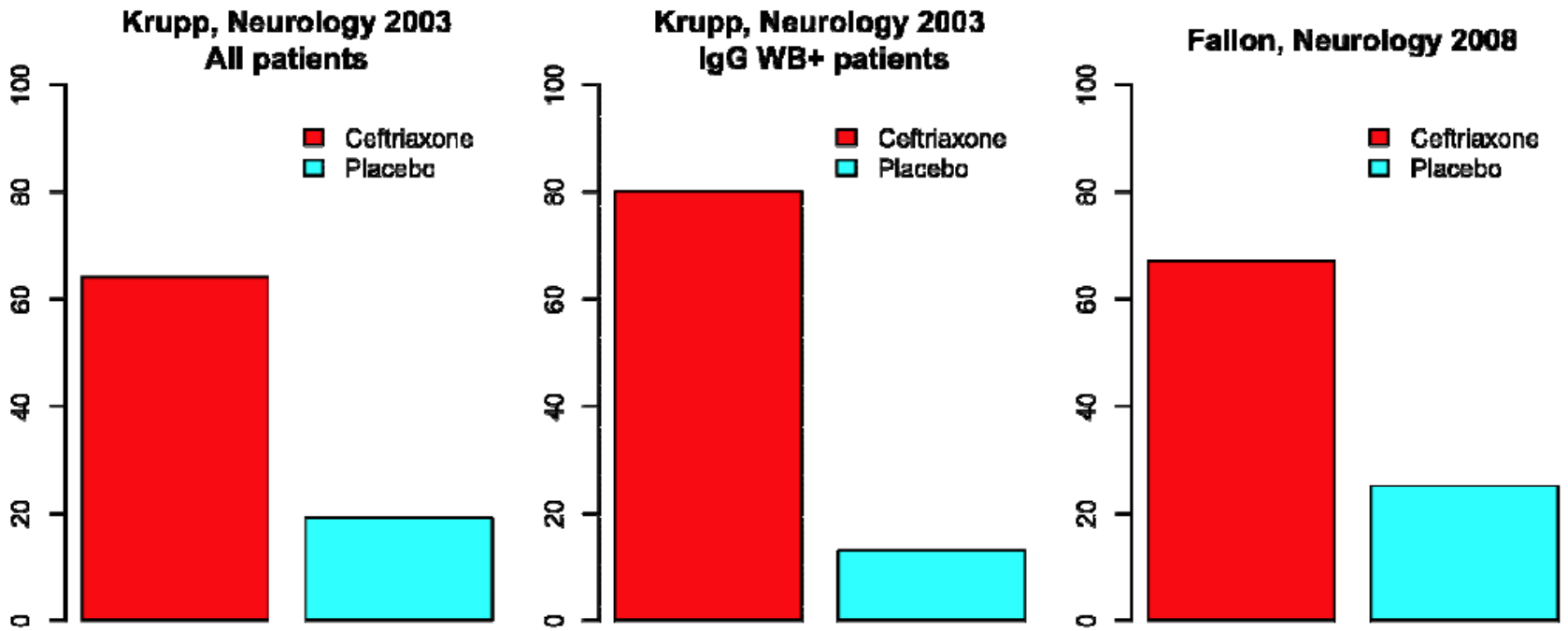


**Fig. (1).** Percentage of Responders on Fatigue Severity Scale in 2 placebo controlled trials of post-treatment Lyme disease.

Fallon B et al, The Open Neurology Journal 2012

# UK evidence for re-treatment

CLINICAL PRACTICE

*Clinical Medicine* 2010, Vol 10, No 5: 454–7

## Lyme disease in the UK: clinical and laboratory features and response to treatment

Richard Dillon, Susan O'Connell and Stephen Wright

# UK evidence for re-treatment

CLINICAL PRACTICE

*Clinical Medicine* 2010, Vol 10, No 5: 454–7

## Lyme disease in the UK: clinical and laboratory features and response to treatment

Richard Dillon, Susan O'Connell and Stephen Wright

- Small naturalistic study: London Teaching Hospital
- Retrospective from case records
- N=77/65 Between 2007-2012
- Most were early Lyme disease (91% EM, 28% neurological symptoms, 4.6% cranial nerve palsies)
- 11 negative ELISAs sent to Reference Lab → 6 of these had positive immunoblots. 44/64 confirmed by immunoblot
- Doxycycline 200mg/day 14-21 days

# UK evidence for re-treatment

CLINICAL PRACTICE

*Clinical Medicine* 2010, Vol 10, No 5: 454–7

## Lyme disease in the UK: clinical and laboratory features and response to treatment

Richard Dillon, Susan O'Connell and Stephen Wright

- Small naturalistic study: London Teaching Hospital
- N=24 6-8 week FU: 1 negative antibody titre, 18 reduced antibody titres, 3 unchanged/stronger
- N=3 (4.6%) treatment failures at 6-8 week stage
- N=1 re-Tx again with IV ceftriaxone 2g/day 21 days
- 11 negative ELISAs sent to Reference Lab → 6 of these had positive immunoblots. 44/64 confirmed by immunoblot
- Doxycycline 200mg/day 14-21 days

# Case Y: An unusual presentation

- 22 year-old veterinary nurse
- No previous psychiatric/medical history
- Sudden onset of severe derealisation/depersonalisation symptoms: May 2016
- Increasing episodes of macropsia/micropsia accompanied by a sense of time-distortion x 3-4/day
- Admitted to hospital June 2016 for physical investigation
- Routine Ix including brain scan and LP normal
- Referred to psychiatry: Provisional diagnosis "Dissociative Disorder"

# Case Y: "Curiouser and curiouser"

"It was only because her psychiatrist was strongly suspicious that something had been missed that we demanded a complete print out of all her test results."

Diagnosis: Alice in Wonderland syndrome
Organic cause highly likely

Lyme serology results:

- June 2016 C6 EIA = Positive (1.461)
  IgM Negative with 2 sub-threshold bands: VlsE(53), Osp17(50)
  IgG Negative with no readable bands
- July 2016 C6 EIA = Positive (1.685)
  IgM Positive with 3 positive bands: VlsE(129), Osp17(200), OspC(170)
  IgG Negative with no readable bands

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# Case Y: Outcome

- GP re-tested Lyme serology, treated with doxycycline with partial response. Referred on for a specialist opinion
- Seen by an Infectious Diseases Consultant
- Slowly responded to treatment with 3 weeks IV Ceftriaxone

Feedback from Mother 02/04/17:

"It now seems a distant surreal nightmare that she had this incredibly swift descent into hallucinating bizarreness last summer, as she's seems to us entirely back to normal - the relief is overwhelming as you can imagine"

# Case Z:?Effect of early antibiotics

- 52 year old woman. Working full-time for a major company
- Bitten: June 2013 South Downs followed by a “spreading rash”
- Day 4: Flucloxacillin 500mg qds 1 week
- Day 11: Erythromycin 500mg qds
- Rash continued to spread (5 x 6 ins). Admitted to hospital with IV antibiotics for 24 hrs
- Lyme serology negative

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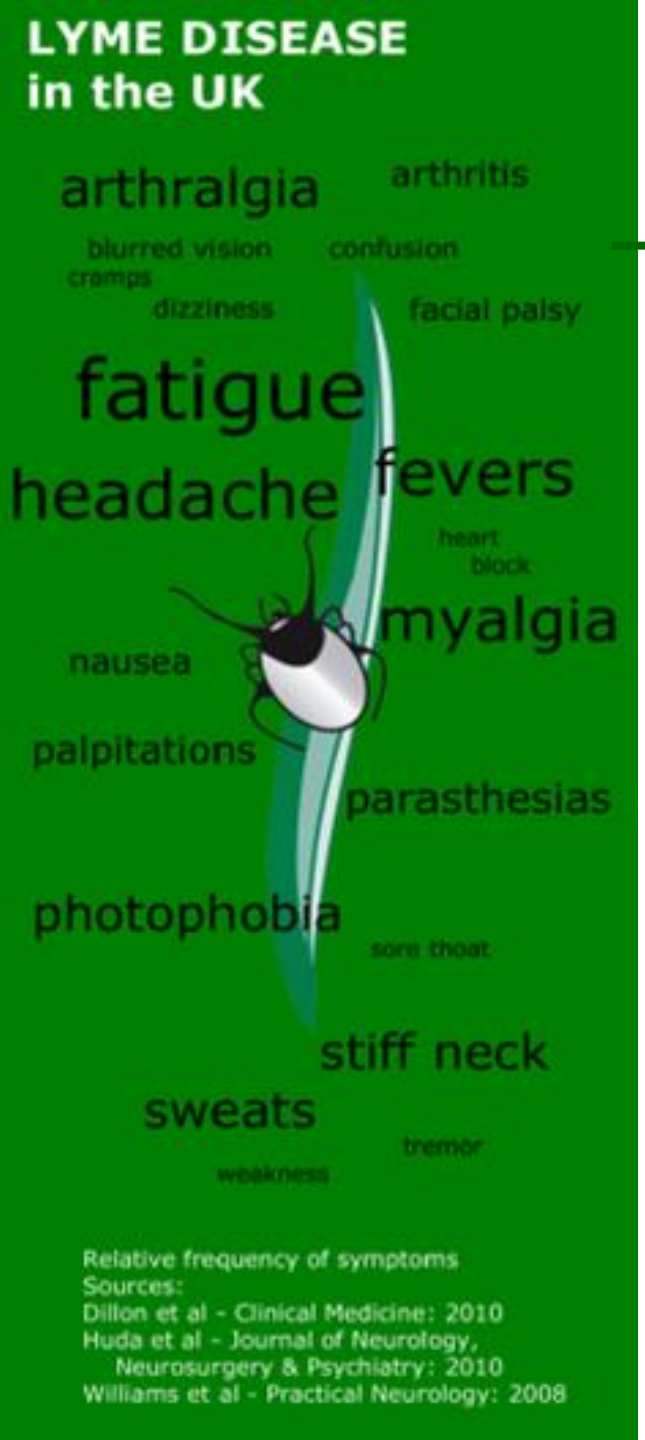
# Case Z:Outcome

- 1 week Flucloxacillin qds and then Amoxicillin 1g tds
- Day 26 v tired, unable to walk far. Tried phased return to work
- Day 63 positive blood test
- GP prescribed doxycycline 21 days, 3 days at 200mg bd the rest at 100mg bd
- Discharged ID. Continues to be seen by immunology for fatigue
- Phased return to work - managed part time
- Continued to improve but Jan 2015 relapse of numbness and paraesthesia
- Feb 2016 Completed 28 days IV ceftriaxone 2g/day – positive improvement. Phased return to work
- March 2017: Minimal symptoms. Back at work part-time, aiming for return to full-time in due course




# Clinical Challenges

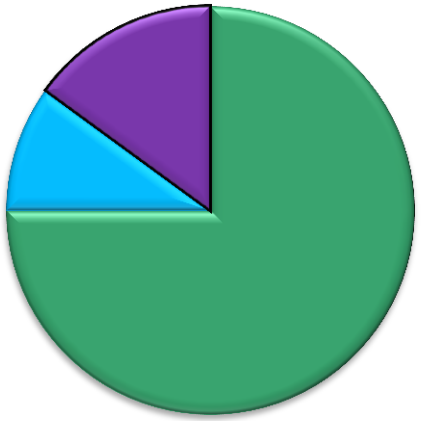
- Non-specific, subjective symptoms. Overlap with other conditions
- Lack of clear case definitions
- Limitations of current tests
- Genuine uncertainties in diagnosis/treatment
- Uncertainties regarding the nature of symptoms remaining or recurring after treatment
- Limited clinical experience with complex cases

# Post Treatment Lyme disease
# What are we treating?

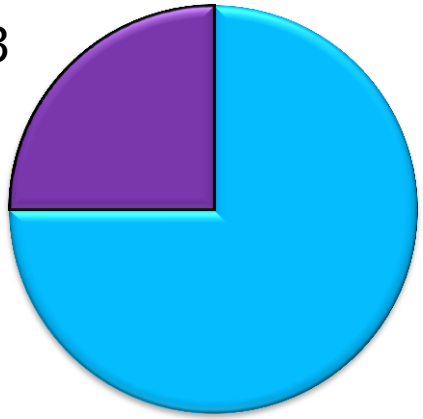
The hypothetical patient:

Patient 1

Patient 2



Patient 3



**Green: Persistence**
**Blue: Auto-immunity**
**Purple: Tissue Damage**

Personalised medicine

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# The way forward?

- Improved awareness
- Recognition of the limitations of diagnostic tests
- Specialist service provision
- Prospective trials of tests/treatment in a clinical context
- Inclusivity

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# Codesign for improved outcomes

Lyme Disease Action

## Striving for the prevention and treatment of Lyme disease and associated tick-borne diseases

## Thank you for listening

www.lymediseaseaction.org.uk

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