

PHE Lyme Disease Open Day

March 25th, 2015

Copthorne Tara hotel, Kensington, London

Welcome & Introduction

The Countess of Mar

Lady Mar welcomed everyone to the PHE Lyme Disease Open Day, which was being held 18 months after the last one. She thanked Tim Brooks and his PHE team for their work so far in trying to build bridges amongst a community of patients, researchers and doctors which had been very divided into 'them and us'. She added that Tim and his team had been under considerable pressure in the last year due to the UK commitment to respond to the Ebola outbreak in West Africa.

As GPs have limited time to assess patients they tend to depend on test results at the expense of subtleties in the patient's condition. Patients who seek help outside the NHS report feeling listened to and treated. Lady Mar suggested that a trial to directly compare the UK test approved by the NHS with tests available overseas would set a lot of minds at rest. There is work still to be done around seronegativity in Lyme disease; to facilitate this and the other known gaps in our knowledge it is important to work as a team.

Chair's Welcome

Dr Jenny Harries, PHE Regional Director, South of England

Dr Harries echoed the sentiments of Lady Mar in welcoming everybody to the meeting. She explained that the date of the meeting had been brought forward due to restrictions on the communication activities of government bodies in the period immediately before and after a general election.

Overview of PHE activities

Dr Tim Brooks, Clinical Services Director, PHE Rare & Imported Pathogens laboratory (RIPL)

Dr Brooks thanked the speakers, some of whom had travelled considerable distances to attend the event, which was timed to raise awareness of issues around Lyme at the start of the 2015 tick season.

RIPL work on a range of diseases, the disease courses of which are rarely 'cut and dried'. In many diseases there is a question mark around how to resolve persistent, post-treatment symptoms and there is a lot we don't know in this area. In order to provoke financial commitments and changes in policy, you need evidence, and generating evidence costs money. Therefore you have to start small and build credibility in order to target progressively larger pools of research funding. The Health Protection Research Unit in Emerging and Infectious Zoonoses (EIZ HRP), a collaboration between PHE and the University of Liverpool, includes within it the first external research funding that PHE has been able to secure for Lyme disease, in the form of one PhD studentship, looking at novel biomarkers of Lyme disease and 50% of a postdoctoral researcher looking at the public and patient perceptions of Lyme disease. A second PhD student, funded by PHE, will look at alternative diagnostics e.g. high-volume PCR.

The Scottish view on Lyme disease

Dr Roger Evans, Consultant Clinical Scientist, Raigmore Hospital, Inverness

Scotland has seen the number of seropositive Lyme disease cases increase year-on-year since 1996. Seroprevalence varies in the different regions, being highest in the Highlands and lowest near the English border, despite a high level of agricultural activity. Travel within Scotland means that wherever they live, people are still exposed to different risks of Lyme. Dr Evans' team has secured funding to develop a real-time Lyme risk map for Scotland.

In Scotland there has been considerable improvement in the quality of clinical data associated with samples tested for Lyme. What is now needed is an estimate of costs of Lyme disease, both the financial cost to the NHS in primary and secondary care and also the financial and human costs borne by the patients. Once these costs are recognised, it is easier for decision-makers to commit resources to tackling the issue associated with prevention, diagnosis and treatment of Lyme. One key improvement would be to make Lyme a notifiable disease and this would help to give a better picture of its true incidence.

Dr Evans highlighted the current lack of a test for current infection – in endemic areas such as the Scottish Highlands, patients may present as seropositive, but that is no guarantee that their seropositivity is related to their presenting symptoms, as it may relate to previous exposure. Increasing the familiarity of GPs with clinical signs such as erythema migrans improves the diagnosis of early Lyme; additionally Scotland are currently developing a novel enzyme immunoassay (EIA) to try and get an earlier diagnosis of Lyme, and hope to have the first results in around 6 months' time.

Ecology of tick abundance and *Borrelia* prevalence

Dr Jolyon Medlock, PHE Head of Medical Entomology and Zoonoses Ecology (MEZE)

Dr Medlock gave a general introduction to tick species and tick abundance in the UK, talking also about the tick life cycle and the roles of different wildlife hosts. He introduced PHE's nationwide tick surveillance scheme, in which ticks are collected from different geographic areas and tested to see if they carry tick-borne pathogens.

Geographic distribution of *Borrelia* is complex; some areas have very high numbers of *Ixodes ricinus* ticks but all are *Borrelia* negative, and where *Borrelia* is found, there is regional variation in which species dominate. Overall, Southern England is still the UK 'hot spot' for *Borrelia*.

Urban expansion into green spaces and wildlife incursions into urban areas have increased the incidence of *Borrelia*-infested ticks in urban green spaces such as parkland. Knowledge of the current incidence of ticks and tick-borne pathogens, combined with data on different vegetation cover can be used to estimate risk factors and inform local authorities, for whom facing up to urban ticks requires a significant shift in mindset.

PHE Tick awareness campaigns

Maaïke Pietzsch, Senior Project Scientist, Medical Entomology and Zoonoses Ecology (MEZE)

MEZE have produced a number of tick awareness materials explaining tick awareness, tick checks and removal. The group conducted a local tick awareness campaign in Wiltshire in 2014, in which a number of media were used to promote public awareness. Evaluation of the campaign showed that the leaflets were the most successful communication method of the ones used. Attendance at local events enabled collection of direct feedback on what worked and what didn't; future tick awareness material in development includes resources for schools (targeting Key Stages 1 & 2) and for outdoor groups.

The Tick Recording Scheme run by MEZE allows members of the public to send in ticks they have found in the course of their daily life, along with geographic information. This enables speciation of the tick and mapping of species distribution, along with banking of the ticks for future analysis of the pathogens they may carry. Volunteers have also been recruited to carry out vegetation sweeps to collect higher numbers of ticks in selected areas.

Keynote address: A review of recent evidence on long term consequences of Lyme Disease

Brian Fallon MD, Director, Lyme and Tick-borne Diseases Research Centre, Columbia University, USA

Dr Fallon began by acknowledging the role patient groups have had in spreading the Lyme awareness message in the US and the UK.

Relatively few studies have looked at Lyme patients with chronic symptoms. In a recent study of post-treatment Lyme encephalopathy patients at Columbia, they looked at the effects of a 10-week course of intravenous antibiotics (versus placebo) on cognition and memory. The study had conservative entry criteria for the test group, requiring demonstrable cognitive impairment, current IgG seropositivity and a previous IV antibiotic treatment lasting at least 3 weeks. Cognitive function in the test group improved significantly on 10 weeks of antibiotics relative to the placebo and healthy control groups, but relapsed within 12 weeks after finishing treatment. Greater improvements were associated with greater severity of starting symptoms. The narrow criteria in the Columbia study may mean the results are less generalizable to other persistently symptomatic patients.

Dr Fallon then discussed his results in the context of two other U.S. randomized placebo-controlled trials, Krupp (2003) and Klempner (2001). The results of the three studies were not in total agreement but there was evidence in both Fallon and Krupp's studies that a repeat course of antibiotics could be effective against persistent symptoms such as fatigue. However, efficacy does not always lead to a clinical recommendation being made as the benefits have to be weighed up against the risks such as severe side effects of antibiotic therapy. Patients & physicians should discuss together the risk/benefit ratio of retreatment. Alternative treatments, for example targeting the immune activation that is present in many patients with PTLs, are needed for those who are no longer benefiting from antibiotics.

Finally Dr Fallon recommended that guidelines should revise their assessment of the U.S. clinical trials - as retreatment with IV ceftriaxone has been shown to reduce fatigue in post-treatment Lyme disease syndrome.

Neuroborreliosis: Challenges and experiences from Norway

Randi Eikeland, Head of National Advisory Unit for Tick-borne diseases, Sørlandet University

Norway has highly *Borrelia*-endemic areas, with *B. afzelii* being the dominant strain. The second most commonly acquired tick-borne disease is Tick-borne Encephalitis. Seventy percent of disseminated Lyme disease in Norway manifests as neuroborreliosis, with 10-50 % of neuroborreliosis patients having persistent symptoms after treatment, notably fatigue and altered cognition. Evidence of thecal antibody and increased protein in the cerebrospinal fluid (CSF) is often demonstrated in persistent infection .

The role of the National Advisory unit is to systemize and distribute knowledge about tick-borne diseases, help establish clinical guidelines, organise symposia, teaching courses and advice for health care professionals.

In a Norwegian cohort study they found that Lyme neuroborreliosis may reduce health related physical and mental quality of life 30 months after recommended treatment. Risk factors for long-term persistence of symptoms were having symptoms for >6 weeks before treatment, more severe disease before treatment and non-recovery at 4 months post-treatment. However, there were no signs of persistent *Borrelia* infection in the CSF in patients with persistent symptoms.

A programme for comprehensive review of potential diagnostic tests for Lyme disease

Dr Sue Best, Director, National Serology Reference Laboratory, Australia

The National Serology Reference lab was established in the 1980s in response to the growing HIV threat. Consequently, the unit has considerable expertise in the development, validation and use of serology tests for HIV and other blood-borne viruses and runs national quality control programmes for diagnostic tests.

Lyme disease is sometimes seen in travellers returning to Australia. A few reports of potential domestically-acquired cases in Australia exist, but the positive test could not be replicated using recognised testing algorithms. Australia does not have *I. ricinus* ticks, and despite several studies of the native tick species, none have yet been found carrying *Borrelia*.

Few labs in Australia currently offer Lyme testing; those that do use largely commercial tests but a few in-house tests exist. Some specimens sent to the US/Germany for confirmatory testing got different results, leading to an increased focus on test validation and Quality Assurance. The reference lab is planning a study to compare serology assays and assay combinations used in Australia, the US and Europe (including the UK NHS test) to elucidate the relative performance of these assays. Interpretation criteria will also be compared, with all assays being interpreted using the manufacturer's criteria, the US CDC criteria and any other criteria used by the collaborating labs. It is hoped that by testing in excess of 1000 positive and 1000 negative samples the study could have the power to detect small differences in performance with greater confidence. However, funding has not yet been secured for the study. Even if the highest performing test or combination of tests becomes clear, it is still vital to obtain high quality clinical information to be interpreted alongside the serological test results in order to make a diagnosis of Lyme.

Working Together?

Stella Huyshe-Shires, Lyme disease Action

Ten years ago the relationship between the healthcare sector and the Lyme patient community was poor - it was an 'us and them' situation. Patients were frequently accused of being anti-science.

Lyme disease Action supported a James Lind Alliance study in which patients and clinicians agreed the top ten uncertainties in Lyme disease which need further research as a priority. This exercise marked a turning point in patient-NHS relations, further improved by the willingness of the PHE RIPL lab at Porton Down to engage with LDA. There have been successes and failures in efforts to work together to manage complex cases. It seems that hospital consultants and the British Infection Association are the groups least willing to change their position on the management of complex Lyme cases. Additionally there are groups within the patient community who engage only with like-minded individuals who reinforce the views they already hold. To move forward, all parties have to be willing to listen to views which are not their own and initiate open dialogue which can lead to real improvements in medical education, diagnostics and patient management.

Panel Q&A

Panel: Tim Brooks(TB), Brian Fallon (BF), Sue Best (SB), Randi Eikeland (RaE) and Roger Evans(RoE)

Chair: Jenny Harries (JH)

Participants had been invited throughout the meeting to submit written questions and leave contact details so that those questions which could not be covered in the Q&A session for time reasons could be followed up on at a later date.

Before the Q&A session began, a patient, Mr Demetrios Loukas, was granted time to address the audience. He told his personal story of fighting to get diagnosed and treated, and explained the huge personal and financial cost to patients if Lyme cannot be reliably diagnosed and treated. Mr Loukas thanked Tim Brooks and PHE for attending the Lyme Parliamentary meeting in January, for organising this open day and for agreeing to meet Dr Armin Schwarzbach and Dr Chris Newton in June to discuss possible research studies.

Q1. How do IgM deficiencies affect treatment outcomes in chronic Lyme patients?

BF: In general terms, IgM is the initial relatively non-specific shotgun immune response, while IgG is the more specific response which normally starts to come up 2-5 days after the IgM and hones itself over subsequent weeks. Reinfection with the same pathogen would produce an IgG response straight away.

TB: In Lyme disease, the immune response does not always proceed in this 'normal' way - *Borrelia* has lots of surface antigens and can evade the antibody response, prolonging the illness.

Q2. Given uncertainties around testing and treatment, how can we increase awareness among clinicians of the limitations of current guidance (how can we get clinicians 'back on the fence')?

RaE: In Norway engage them in research, run annual education courses and produce leaflets to inform GPs and the public.

BF: Doctoring is a vocation – lots of training and enthusiasm for the role but not always first-hand experience of every condition. Doctors will always look to the recommendations of expert guidelines. Quality research from highly regarded scientists is needed to change expert guidelines. That takes time and funding, but it is starting to happen in the US with recent animal studies.

TB: Funding bodies need to be convinced of the need to generate new evidence, especially when opinion leaders have previously stated that it is not needed. In the UK we are heading in the right direction with questioning of the current guidelines. We can write to doctors but we can't make them read what is sent, however a higher media profile means that patients are more aware and that motivates GPs to become more informed themselves.

RoE: We need to demonstrate the financial and human cost of Lyme to the decision makers so that they sit up and take notice.

Audience comments:

- Quantitative and objective physiological measurements – we have the technology to quantify these but it is time consuming; the role of the autonomic nervous system may be the elephant in the room.
- The Royal college of GPs engaging with the LDA e-learning module but so far only low numbers of participants. How do we increase uptake?
- PHE/DH should run a newspaper/TV/radio campaign instead of holding meetings.
- There are still areas where there is no signage in the countryside to make people tick-aware. Awareness also needs to include urban areas such as parks.
- Public awareness of ticks and Lyme disease could be raised through education targeting schools, local authorities, parish magazines etc
- Lyme disease should be notifiable: DH and PHE looking at making this happen
- Can we reward GPs for Lyme diagnoses?
- Can we have a way to enable GPs/consultants to treat people with negative Lyme tests?
- GPs don't want to be held liable for patients being given antibiotics when they don't have Lyme in case of serious side effects. This makes patients feel ignored.
- UK guidance should cover how to manage patients with negative Lyme tests
- Tick removers (or tick cards) need to be more widely available, including out of hours as prompt tick removal is key. Scotland are looking to increase availability of tick removers.
- PHE needs to be more creative in its use of different information and social media
- Charities may be able to get interested creative/digital marketing firms to do Lyme awareness work *pro bono*

TB: PHE RIPL try to engage the media whenever we can, by accepting requests for interviews etc. However we have nowhere near enough funds to mount mass media campaigns such as TV adverts. We can try to engage with local authorities and empower them to promote the tick awareness message. Making Lyme notifiable will catch at most around 50 % of Lyme cases which meet a particular case definition of the illness. This is still better than the current case reporting. In the UK we do not have any high-profile

celebrity Lyme patients or advocates – they can be powerful in increasing awareness of diseases and conditions. PHE is looking into how to make greater use of social media and local authorities to spread the tick awareness message.

Q3: What do we expect clinicians to do with symptomatic patients in the face of negative serology or conflicting serological test results?

SB: if a disease is made notifiable it has to have a case definition. Is it really feasible to create a case definition of Lyme which excludes serology? Transparency around the validation data for the different tests available in different labs is needed. We need to look at improving the sensitivity of PCR as an alternative test for early infection.

BF: Prompt treatment with antibiotic increases the chance of a good treatment outcome but clinicians have a duty to 'do no harm' and wrongly prescribing antibiotics can be serious, even fatal. Most clinicians can be expected to weigh up the risk:benefit ratio carefully before deciding on treatment.

The CDC has said that diagnosis of Lyme is a clinical diagnosis supported by serological tests. Their criteria for surveillance are much stricter and can be misused by clinicians as diagnostic criteria. In hyper-endemic areas they sometimes treat summer 'flu symptoms with antibiotics straight away before testing. This is based on assessment of the Lyme risk in those specific areas; IDSA don't recommend it as a general measure.

Audience comments:

- The key group to engage in this is the consultants in secondary care

Q4: Does anyone think there is a place for looking at novel drugs?

RoE: The financial and human cost burden of Lyme need to be better understood before research funding becomes available for Lyme. This is unfortunately a slow process.

TB: we need good quality clinical trials and data. We need to look into other possible diagnoses for patients displaying Lyme-like symptoms but who test negative. We need to raise public awareness so the research councils put out the right funding calls so that research funds become accessible.

SB: we need new commercial tests. We need open and clear validation data for the tests being used.

BF: In the US Lyme is high in super-rich areas so there is lots of private funding for research. What is needed urgently is a test for active Lyme infection. Additionally, Permethrin-infused clothing to prevent tick bites is an exciting invention.

RaE: If we treat acute disease better we will solve a lot of problems, then we need to study the immune system of the treatment non-responders. This will point to new therapies.

Q5: Why does the Norwegian case definition of neuroborreliosis require pleocytosis of CNS?

RaE: Because this is considered a characteristic feature of untreated neuroborreliosis. It restores very rapidly upon treatment with antibiotics (usually oral but sometimes IV if indicated).

Q6: There is contradictory evidence around long term antibiotic therapy. Other therapies e.g. immunoglobulin therapy have been suggested. When will patients with long-term disease get offered something new or different on the NHS?

BF: Clarified that he does not advocate long term antibiotics, his research shows some evidence of benefit to repeated courses of limited duration.

Efforts should be focused on developing clear diagnostic criteria and better testing, including tests specifically for active Lyme disease.

Wrap up

JH: We are all mutually interdependent in advancing the cause of better diagnosis, management and public awareness of Lyme disease. There are uncertainties due to gaps in the evidence base – only by working together will we raise public awareness and secure the necessary research studies to make real progress.