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I would like to start by making clear that Lyme Disease Action does not regard itself solely as a patient advocacy group. We are a non-profit organisation striving to improve the prevention, diagnosis and treatment of Lyme disease in the United Kingdom. This is on behalf of everyone: doctors, patients, carers, employers and healthcare providers alike. To improve the position for patients, we have to improve the position for doctors: if doctors are able to recognise, diagnose and treat Lyme disease, and have the means to do this, all other stakeholders will benefit.

In the UK we are affected by the polarisation of views concerning Lyme disease that has arisen from and is epitomised by the IDSA/ILADS controversy. This controversy has, courtesy of the internet, washed across the Atlantic to Europe, affecting all countries but possibly the UK the most because of the common language.

It became apparent to Lyme Disease Action that UK doctors would not take a public group seriously without some sort of official accreditation. We are therefore now accredited to our Department of Health's Information Standard. This means that our information management processes have been verified to make correct, unbiased use of sources of evidence: where there are alternative opinions, or uncertainties regarding evidence, we say so. I shall therefore not just be presenting the patients' views of the challenges, but trying to portray where we feel the problems really lie.

Recorded incidence in mainland Europe is far higher than in the UK, and in E Europe higher than in the USA. This is partly because of better awareness but partly because of the history and epidemiology of the disease itself. However, every country has a different reporting mechanism and so all incidence figures are approximations only.

Across Europe it is notable that there is disagreement on the incidence of Lyme disease and the possible scale of the problem. Papers and websites written by health professionals normally say that over diagnosis occurs and "Public perceptions of the disease in Europe have been distorted by the media and by activist groups".[1] Papers and websites written by members of the public say that Lyme disease is under diagnosed.

Is Lyme disease underdiagnosed? In the UK we do not know the incidence of Lyme disease. Positive blood tests are recorded centrally and these have been rising steadily since records started but nobody knows how many are diagnosed in the early stages from an erythema migrans and no-one knows how many are undiagnosed. An audit at a highly aware GP Practice in Scotland has found an incidence of 370/100,000 population, based on clinical diagnosis of the erythema migrans rash, in contrast to the recorded (laboratory confirmed) 17/100,000 in the surrounding area. (Private communication) Although one practice is a small sample, it seems perfectly possible from this that 95% of cases are not entering our official statistics: a few because they are diagnosed without a blood test; the majority because they are simply not diagnosed at all. Applying this figure (of 95% possibly not being recorded) leads to an estimated 24,000 cases per year in the UK. The Health Protection Agency (HPA) estimates up to 3,000 diagnosed early with erythema migrans and this would leave about 20,000 cases of undiagnosed, untreated Lyme disease cases per year. This, for a disease that is treatable with cheap antibiotics, places a large unnecessary burden on state healthcare and benefit costs.

Is there evidence that Lyme disease is over diagnosed in the UK? A recent paper retrospectively analysed the case notes of all patients referred to a major infectious diseases clinic in the NW of England over a 5 year period (n=115) for consideration of possible Lyme disease.[2] The abstract reports that out of all the patients only 23% (n=27) were diagnosed by the clinic as having active or previous Lyme disease, whereas 33% (n=38) were diagnosed by

the clinic with Chronic Fatigue Syndrome (CFS). The authors state that these figures mirror similar studies in N America and voice their concern that patients with CFS are susceptible to misdiagnosis and inappropriate treatment, particularly in private settings. This analysis does appear to support the idea that Lyme disease is misdiagnosed in some cases in the UK, but it should be appreciated that the total number of patients was small and the number of patients found by the clinic to have been misdiagnosed with Lyme disease in the whole 5 year period was a mere 42.

Lyme disease is not alone: many diseases and conditions are misdiagnosed. Putting it in perspective, a similar survey of patients referred to a specialist CFS clinic in NE England found that over a single year 40% of the patients did not have CFS - 48 in one year. 47% of these were suffering from fatigue associated with a chronic disease.[3]

The challenge here is for everyone to stop beating their own particular drum and ask <u>why</u> Lyme disease is difficult to diagnose and whether anything can be done about it.

Because of the state funded National Health Service in the UK, money is less of a direct healthcare issue than in the USA. Doctors in the UK simply want to be able to diagnose and treat their patients effectively. Diseases and conditions that are rare and difficult to diagnose take doctors time and effort. They need unequivocal tests and clear guidelines so that they can do their job for their patients. Unfortunately neither of those exists in the UK for Lyme disease.

In a small country, with a relatively low incidence of Lyme disease, most UK doctors have not seen enough cases to gain much clinical experience and so there is heavy reliance on the tests. When a test result is returned, the doctor is likely to telephone the laboratory for advice and because the majority of confirmatory tests have until recently been conducted at one particular reference laboratory it is this laboratory which came to be seen as the expert source of knowledge in this country. The head of this HPA laboratory served as consultant to the IDSA panel in development of the 2006 guidelines and has collaborated with other IDSA authors in papers, and so it is understandable that the views of IDSA have prevailed in the UK.

The HPA has issued information packs and website pages with references encouraging doctors to believe that internet sources of information are unreliable, that the dangers to patients from misdiagnosis are considerable and that tests from non UK laboratories are unaccredited and therefore unreliable. All of this has an element of truth: some internet sources are not based on science at all, one patient has died from inappropriate treatment (in the USA) and some non-UK laboratories offer tests that are no more a specific indicator of Lyme disease than is a very swollen knee. These facts are a concern to all of us but drawing attention to only this side of the coin is a misrepresentation of the state of affairs.

A small number of UK doctors, led by microbiologists concerned that serology was being questioned, have drawn up under the auspices of their professional organisation the British Infection Association (BIA), a Position Paper on Lyme Disease and published this in their own journal.[4] This paper fails to take a balanced and unbiased view of the literature and is inadequately referenced. It is, however, referred to by the HPA and by doctors across the country to support the view that Lyme disease can be definitively diagnosed by serology and that it does not persist after "recommended" treatment: it attempts to reassure BIA members that there is not a problem.

Unfortunately, European research shows otherwise. Several studies have looked at various blood tests used in Europe and found differing results depending on which tests are used.[5] Doctors do not have time for critical reading, however, and understandably trust that their peers within the BIA will have done a good job of drawing up some guidance.

Europe faces the challenge of more than one species of *Borrelia burgdorferi* sensu lato and this adds a complexity to serology tests which rely on detection of heterogeneous antigens. The

Lyme reference laboratory in Scotland uses its own in-house Western blot, using native antigens and far more bands than are used in commercial test kits. In an acknowledgement that even the best test is not perfect, they also include response to treatment in the diagnostic path.[6] No laboratory undertakes extra work like this without good reason.

The clinical presentation may also be more complex in Europe. It has been shown that *Borrelia garinii* causes what, in Europe, is appreciated as typical early Lyme neuroborreliosis (Bannwarth syndrome), whereas the clinical features associated with *B. afzelii* are much less specific and more difficult to diagnose.[7] In the absence of a definitive test it is not surprising that many cases are un-diagnosed.

When it comes to treatment, the UK follows IDSA guidelines in asserting that there is no evidence of persistence following recommended antibiotics and refers to USA papers which have claimed no benefit for prolonged treatment. This is despite evidence to the contrary in UK case studies where patients have required more than one course[8] and European research studies showing survival of Borrelia in previously treated patients.[9] It also flies in the face of European guidelines for Neurological Lyme disease[10] which point out that there have been no good quality European trials on agent, dose or treatment length; that treatment recommendations are, in fact, based on opinion not evidence.

In most other diseases, if a patient relapses, there is no question of withholding a further course of treatment, even if the symptoms are subjective. In Lyme disease it appears that patients must prove, by objective signs, that they are still suffering: their word is not enough.

Following extensive and critical reading, it seems to us that there are uncertainties in the diagnosis and treatment of Lyme disease but we need to get other sceptical stakeholders to examine this possibility. A small organisation like ours can accomplish very little in the current climate of suspicion and disbelief in patients' views. To attempt to address this, we have started a process, mediated by an organisation funded by the National Institute for Health Research, the James Lind Alliance.

This process involves surveying doctors and patients to find out what uncertainties they have been faced with during consultations. To engage doctors in this has been taxing, to say the least, because many believe there are no uncertainties. It has only been achievable because the British Infection Association, following our criticism of their position paper, realised that their input was important. The collected uncertainties are currently being examined by an independent researcher against the published literature and systematic reviews. This will result in a list of true uncertainties: questions about diagnosis and treatment of Lyme disease to which research has not yet found an answer. This list will then be voted on to find which both doctors and patients agree are the top 10 priorities. Note that word: agree.

The biggest challenge we face globally is probably agreement on the uncertainties. Only then can we, together, prioritise research. There are positive signs that in the UK we are beginning to shake off the IDSA/ILADS shackles. Not only is the BIA working with us on prioritising uncertainties, but the HPA, following a reorganisation and a move of the Lyme disease reference laboratory, has also engaged with us in a joint research proposal. It will take time, but we are moving forward.

The situation of polarisation of opinions along the ILADS/IDSA fault line occurs in other European countries as recently illustrated by an editorial in the Netherlands Journal of Medicine.[11] The Lancet Infectious Diseases published an opinion piece claiming anti-science in patient organisations[12] and inclusion of a UK author will have reinforced the idea amongst readers that "anti-science activists" are causing problems in the UK.

It can be hard not to see the collective publications denying patient rationality as an orchestrated attempt to discredit an alternative view. It is probably, however, simply an

example of confirmation bias and the natural reluctance of people to climb out of an entrenched position.

Lyme Disease Action attended the European Congress of Clinical Microbiology and Infectious Diseases in London in April this year. Discussions with international delegates were revealing. Scandinavian and N European doctors face similar problems to the UK: doctors have little clinical experience and rely heavily on test results. When patients don't believe a negative test result they send to Germany for a CD57 test and believing that a positive result indicates Lyme disease, they demand treatment which may not be appropriate. In E Europe, where incidence of Lyme disease is far higher, doctors have more experience and were telling us "it is a big problem: we don't have good enough tests and we don't know how to treat."

This Congressional hearing is being held because it is perceived that there is a problem with Lyme disease. This is not just a medical problem due to the imperfect state of 21st century medicine, but a Problem with a capital P. A human problem, perhaps, which humans can therefore resolve; if, collectively, they have the will.

To us in the UK there seem to be two principal aspects to the Lyme disease problem: politics and the uncertainties of the science. The first is preventing recognition of the second. Politics, prestige and defence of positions should not obstruct patient care and should not hamper the search for understanding.

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