Vector-Borne Infection Research-Analysis-Strategy

November 2017

Analysis of the NICE Lyme disease draft Guideline Research Recommendations

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A call for Lyme disease research: Be careful what you wish for, you may not get what you expect.

There are recent statements in the NICE guidelines regarding the need for research on Lyme disease. This may be designed to placate those unhappy with the proposed NICE guideline, or may help fund research projects. However we should temper our joy at the thought that useful research will be carried out to improve our knowledge of the disease and treatment.

Medical research programs can take many years, from definition through approval, data collection, analysis and publication. It is critical that projects and research teams are carefully selected to achieve progress in the field of study.

Over the last 30 plus years of work there have been outstanding and valuable studies from many hundreds of researchers that have generated a wealth of data. Running in parallel there have also been research projects and publications that maintain the status quo of knowledge as defined by a few influential figures in the Lyme world.

A number of facts are clear:

1) Lyme research funding has been miniscule when compared to other diseases such as HIV, Ebola, Zika etc.

2) Many excellent research projects and studies have been carried out, however their findings are ignored in all UK, EU and IDSA guidelines.

3) Historically Lyme research budgets have been assigned to the same groups over a long period and Willi Burgdorferer who identified the first Lyme disease bacteria in 1984 stated:

> "The controversy in Lyme disease research is a shameful affair. And I say that because the whole thing is politically tainted. Money goes to people who have, for the past 30 years, produced the same thing—nothing."

It can be expedient for organisations to respond positively to stakeholder inputs and recommend research. Be careful what you wish for, you might not get what you expect. Research is a must, good research is not a given.

Introduction to the Recommendations

The number and nature of NICE's recommendations for "high priority" research can lead to only one conclusion: attempting to produce a guideline with so much missing evidence, was an exercise in futility which should not have been undertaken. NICE have wasted thousands of pounds of public money in the production of advice which at best will cause confusion and at worst will harm patients and doctors. NICE have chosen to ignore the clinical evidence of doctors who have treated thousands of patients, but have included some biased and low quality clinical trials as 'evidence'.

NICE do not fund research and they can call for any and every investigation they can think of, and none of it will ever have to be delivered. Aside from the sheer scale of the research that they have recommended, some of the projects conceal hidden agendas. When analysed critically, some of these projects would predictably harm patients and obstruct their proper medical care, and some would be either pointless or even impossible to complete.

When reading the NICE research recommendations, please remember that all of these are supposedly "high priority" for England and Wales. Combined, these two countries have around 1,000 officially reported cases of Lyme disease per year. This equates to an incidence of 1.75 cases per 100,000 population. It is notable that much of the research that NICE recommend has not been done by nearby countries, even though they have incidence rates up to 170 times higher than England and Wales (see Table 1). Yet NICE believe that UK scientists are going to spend millions, researching a disease which Dr Matthew Dryden of Public Health England claims has a 100% cure rate with a short course of antibiotics, and where 'recurrence or relapse' is 'extremely unusual'.

Country	Incidence (new cases per year) per 100k population.	Number of times more cases than England and Wales
England, Wales	1.75	
France	49	28
Belgium	114	65
Netherlands	149	84
Germany	261	148
Austria	300	170

Table 1. Lyme disease incidence with comparison to England and Wales

Research Recommendation #1

The NICE draft guideline states:

1/ Core outcome set for studies of management of Lyme disease

> "Can a core outcome set be developed for clinical trials of management of Lyme disease?"
> "The development of a core outcome set was identified as a high priority because it would allow comparison across trials and allow appropriate meta-analysis to strengthen results."
> **Why this is important**
> Antibiotic treatment is the mainstay of management for Lyme disease. The studies published on the management of Lyme disease use differing outcomes, which are often poorly defined. The development of a core outcome set was identified as a high priority because it would allow comparison across trials and allow appropriate meta-analysis to strengthen results. The method used should be patient-focused and include patient input on priority outcomes and should determine core outcomes and how they should be measured.

Producing a Core Outcome Set and expecting multiple Clinical Trials to adopt those criteria, is in contradiction to other contents of the draft guideline. The NICE draft includes treatment recommendations which have predetermined that most patients will be cured with 3 weeks of a single antibiotic and the remainder will be cured with a further 3 weeks treatment. Therefore, a "core outcome set" is superfluous and the call to establish one is questionable.

"Meta-analysis" is a research method which combines data from multiple clinical trials to effectively make one big trial. E.g., the data from 10 trials with 20 participants each, could be combined to make a virtual trial with 200 participants. As the UK does not have one clinical trial, and most of our neighbouring countries with up to 170 times more cases than us, have not found it necessary to produce a 'core outcome set', worrying about 'meta-analysis' when even the basic research has not been done, is nonsensical.

A possible explanation for this research proposal which would otherwise appear ridiculous, appears to be in order to provide justification for stopping treatment of patients who remain ill following so-called, 'adequate treatment', regardless of whether or not they are still infected. E.g., a core outcome set for Lyme patients might show what Dr Dryden claims for his own research, that Lyme is cured with a short course of antibiotics. According to this principle, if a patient remains symptomatic or relapses after treatment, then they cannot have Lyme disease and can be re-diagnosed with something else, even if that requires making-up a new illness. As a way to guarantee 100% treatment success this would be a Catch-22 that patients with persistent infection could not escape from, even though it is completely illogical.

There is a theory known as 'Test of Treatment' in which an uncertain diagnosis is treated experimentally to help confirm or disconfirm a diagnosis. For this to work, it requires that the treatment can produce a predictable effect. In the case of long-term infection with Lyme bacteria

the effect of antibiotics depends on numerous variables and can be further confounded by co-infections and opportunistic infections. The *Borrelia* family bacteria which cause Lyme, contain some very toxic and immunogenic proteins which can be released when the bacteria is killed, so an immediate worsening of symptoms with antibiotic treatment could be an indicator. However, the effects of the treatment will also depend on the locations and morphological stages of the bacteria. E.g., a patient whose infection is mostly comprised of dormant propagule forms of borrelia, might have a negligible response to doxycycline or penicillin unless the treatment is maintained for months. Factoring-in these and other complexities mean that a Test of Treatment would often require evaluation by an experienced physician specialising in Lyme disease. The same complexities described above, would apply to a core outcome set, rendering a one-size-fits-all criteria, impractical and undesirable if individualised patient care was ever a consideration.

However, if the objective was to get rid of patients and deny them proper medical care, then a core outcome set could be the perfect solution. The criteria would probably show that patients can remain symptomatic for weeks or months and make it possible to claim that it is acceptable and common for patients to remain ill following 'adequate treatment', but that they no longer have Lyme disease and therefore no longer require treatment or care for the infection.

Human Rights issues with Lyme Disease

This makes sense when one understands that a core outcome set would support the re-diagnosis of patients with persisting or relapsing symptoms, which in most other persistent infections would be interpreted as inadequate treatment. Re-diagnosing Lyme disease patients with PTLDS, CFS or CANS, would support Dr Dryden's construction of a new illness which he believes is not Lyme disease and would provide justification to deprive patients of treatment, as well as maintaining Dr Dryden's claims of 100% treatment success.

As a strategy to help save insurance companies a fortune by denying support and treatment for chronically ill Lyme patients and protecting shareholder dividends, this NICE recommendation makes perfect sense. Most wonderful of all (from a profit perspective) is that NICE can recommend this 'high priority' project without it costing a penny to them or the insurance companies who would probably be the main beneficiaries, whilst Lyme disease patients and/or the UK public are expected to fund an enterprise that would predictably deprive many patients of NHS or insurance funded healthcare and support.

Patients that remain ill, or who relapse following 'adequate treatment', can be re-diagnosed with a made-up illness that has no World Health Organisation (WHO), International Classification of Diseases (ICD) coding. This can result in violation of the Human Rights of patients if they are denied care and treatment. The latter issue is part of an investigation by a Special Rapporteur of the United Nations Human Rights Council. One of those providing testimony is Jenna Luché-Thayer, a Human Rights expert with 32 years experience. Jenna states:

"Borreliosis infections are pandemic – these include relapsing fever and Lyme borreliosis. The WHO diagnostic codes do not recognize many of the disabling conditions caused by these infections. Across the globe, medical systems use these codes to diagnose illness and determine treatments. The outdated codes result in very sick people being denied treatment —even when treatment options meet the internationally accepted gold standard for guidelines set by the Institute of Medicine (IOM)."

Legal Action against the IDSA and insurance companies

In an ongoing lawsuit being pursued in the USA against the Infectious Diseases Society of America (IDSA), multiple medical insurance companies and some of their named employees who were responsible for the IDSA Guidelines for Lyme disease (much of which appears to have found

its way into the NICE guidelines), the plaintiffs complaints include some of the factors described above:

"46....Lyme doctors know that if Lyme patients are undiagnosed, or are misdiagnosed with another ailment, the Lyme disease can become so severe that without longterm antibiotic treatment the disease will spread to their joints, their heart, and their nervous system causing crippling muscle and joint pain, disabling fatigue, arthritis, neurological disorders, cardiac disorders, depression, memory loss, bladder loss, bowel dysfunction, visual loss, and death.

47. Initially, the Insurance Defendants provided coverage for Lyme disease patients, covered long-term antibiotic treatment, and even paid for extended hospital stays to treat patients with Lyme disease who did not respond to short-term antibiotic treatment. This allowed doctors to properly assesses and treat patients with chronic Lyme disease and prevented the suffering and death of many thousands of Lyme disease patients.

48. In the 1990's the Insurance Defendants decided that treatment of Lyme disease was too expensive and "red-flagged" Lyme disease. The health insurance industry made a concerted effort to deny coverage for treatment of Lyme disease. The Insurance Defendants enlisted the help of doctors who were researching, not treating, Lyme disease. The Insurance Defendants paid these IDSA Panelists large fees and together they developed arbitrary guidelines for testing Lyme disease.

49. Once these arbitrary guidelines were decided, the Insurance Defendants could, and did, deny coverage for patients if they did not meet their new stringent Lyme testing protocols. Since most Lyme patients would not test positive under the new protocols, the Insurance Defendants could deny coverage for many people suffering from Lyme disease.

50. Additionally, the Insurance Defendants, with the help of the paid IDSA Panelists, decided that long term antibiotic treatment was not necessary and all Lyme disease patients could be cured in less than a month. By August of 1992, the Insurance Defendants had imposed an intravenous antibiotic limit of twenty-eight days.

(With thanks to Dr. Steven Phillips & Dana Parish for identifying these important excerpts.)

At the present time a core outcome set is not needed and is certainly not any sort of priority for doctors or patients. However, it might be desirable to those who against all evidence, deny that chronic Lyme disease exists and might serve the purposes of those who do not want chronic Lyme disease patients to be treated in a similar way to patients with other chronic infections.

Recommendation #2

The NICE draft guideline for Lyme disease states:

2/ Clinical epidemiology of Lyme disease in the UK

What are the incidence, presenting features, management and outcome of Lyme disease, including in women with Lyme disease who are pregnant, in the UK?

Why this is important

There is a lack of robust epidemiological data on Lyme disease in the UK, particularly in people who are immunocompromised or pregnant. A large clinico- epidemiological study to collect data on incidence, presenting clinical features, management and outcome of Lyme disease in community and hospital settings in the UK would generate population-based statistics. These statistics would enable interventions such as antibiotic treatment and service improvements to be assessed properly, and for services to be tailored so they best serve people with Lyme disease; this was felt to be of

> high priority. There is no current requirement to notify cases of Lyme disease, therefore, current data are likely to under-estimate the number of people who are seen and treated in the community without serological testing. The morbidity of those who are not rapidly diagnosed and those who seek and receive non-standardised care outside the NHS would justify the costs of this large study.

Incidence

Identifying the 'incidence' of Lyme disease is not a 'high priority' for research in the UK. Credible data would be interesting, but is not in fact, any more urgent now, than it has been for the past 3 decades during which time the UK authorities have largely ignored the threat of a Lyme disease epidemic. Neighbouring countries with up to 170 times higher incidence than England and Wales do not have 'robust epidemiological data'. Neither do the USA, where the Centres for Disease Control and Prevention (CDC) admit that their true incidence of Lyme is probably 10 to 12 times higher than the number of officially reported cases, e.g., 300,000 to 360,000 per year.

PHE have repeatedly claimed that the true incidence in England and Wales, could be two to three times higher than the officially reported figure of ~1,000 cases per year. Believing that the UK detects one-third to one-half of cases would make UK Lyme disease surveillance 3 to 6 times more efficient than that of the USA, a preposterous claim (please see the VIRAS analysis of UK incidence). The immediate need is for Public Health England to admit that Lyme disease is grossly undetected and unreported, and that this is a problem that needs addressing with ***routine*** surveillance and rational estimates, not wishful thinking and expensive research which is of low priority compared to the urgent needs of UK patients.

A genuine priority for UK research is to investigate the ***prevalence*** of chronic Lyme disease. The weak management of Lyme disease in the UK has created the illusion that it is rare and of little concern to the public or to doctors. As a result, the vast majority of cases have gone undiagnosed and untreated. So by now, the UK has tens or hundreds of thousands of patients living with chronic Lyme disease. Those who are chronically infected and symptomatic will inevitably have been misdiagnosed with something else, e.g., M.E., CFS, MS, Fibromyalgia, Parkinson's and other diseases. Many of these patients will be enduring terrible suffering and must be detected and treated as a genuine 'high priority'.

"management and outcome of Lyme disease"

Studying these is not possible without a reasonably accurate method for identifying cases. As PHE do not acknowledge any of the sophisticated tests that can help to identify true cases, including those which are negative by NHS testing, this whole recommendation is revealed to be meaningless bluster. The exercise as it is described would predictably maintain the current gross underestimation of incidence and ignores prevalence altogether. This may be acceptable to PHE who appear to enjoy ridiculous Lyme disease statistics but would do nothing for patients, doctors or the public.

"including in women with Lyme disease who are pregnant"

One could be forgiven for wondering why this was incongruously tagged onto the end of this recommendation. If the idea was to convince us that this issue is taken seriously, then it is a massive FAIL. Those that appreciate the possible consequences of Lyme during pregnancy will recognise that ***this is a priority which fully justifies it's own dedicated research.*** This will not be achieved by lumping it together with a load of stuff and nonsense.

Conclusion

The NICE draft guideline Research Recommendation #2 is ill-conceived and disingenuous. It is actually shameful.

Recommendation #3

The NICE draft guideline for Lyme disease states:

3/ Seroprevalence of Lyme disease-specific antibodies (and other tick-borne infections in the UK population)

> What is the current seroprevalence of Lyme disease-specific antibodies and other tick-borne infections (such as babesiosis, ehrlichiosis, anaplasmosis, bartonellosis or Q fever) in people in the UK when performed using UK-accredited assays (ELISA based on C6 antigen and immunoblot)?
>
> **Why this is important**
>
> This information is not currently available and is of high priority. Without understanding the underlying population seroprevalence of Lyme disease-specific antibodies in the UK, it is impossible to interpret incidence data accurately and to understand fully the epidemiology of Lyme disease in the UK. The available data suggests there are areas of higher and lower prevalence in the UK but with many gaps in knowledge. The information will help to interpret serology of individuals living in endemic areas, where positive serological results may be more common and may not always indicate an acute or recent infection. This will be of benefit to patients and healthcare workers in the UK treating or affected by Lyme disease. Many patients are concerned about the possible presence of co-infections transmitted by ticks: these are thought to be rare in the UK (compared to, for example, the east coast of US) but we have no data to confirm or refute this. Better evidence may improve diagnostic and treatment decisions.

Seroprevalence is irrelevant compared to the serious issues

Given the urgent need for improvements in patient care for Lyme disease in the UK, this gormless recommendation beggars belief. NICE have again compounded entirely separate issues (in this case seroprevalence and coinfections), suggesting that they do not actually take either of these seriously. Furthermore, contrary to what NICE claim, 'seroprevalence' is largely irrelevant to the care of patients who are suffering illness caused by Lyme. The project as described would in fact predictably obstruct the care of Lyme patients, but it would support Public Health England and their policy of denying treatment for Lyme disease, even for patients with positive NHS tests.

This research would produce predictably misleading information, especially in view of the proviso for using tests that are known to be inaccurate. This statement appears to show a willingness to make concessions to the concerns of patients. However, when read in the context of the remainder of this draft guideline and the historical claims of PHE and the HPA, it can be recognised as just another ruse to protect those responsible for the incompetent management of Lyme disease. Furthermore, it facilitates those who wish to enforce antimicrobial stewardship on doctors and an unsuspecting patient population, and maintain the illusion that regarding Lyme in the UK – everything is under control.

Claiming that this is 'high priority' appears to be in order to create an impression that Lyme disease is being taken seriously. Whereas the predictable result of this stratagem would be to show that healthy people are seropositive in substantial numbers – just as has been found in other countries. This would aid RIPL and the former Reference Laboratory at Southampton to defend their disgraceful record of obstructing the diagnosis of patients requiring treatment, but do nothing for doctors or their patients who suffer serious and chronic illness due to infection with Lyme bacteria.

E.g.: "Screening of IgG antibodies against *B. burgdorferi* in blood donors as a proxy for the presence in the healthy population showed seroprevalences of 2.7% both in Hamburg and Bavaria [16], [17]. In France (3.2%) [18], Italy (4.9%) [19] and Romania (4.3%) [20], similar proportions of seropositive individuals among blood donors were assessed. In population-based

surveys, higher seroprevalences were seen in Germany (Berlin: 8%, n = 3,736 [21]; Bavaria: 15%, n = 4,896 [22]; Baden-Württemberg: 16.9%, n = 1,228 [5]) and Finland (19.3%, n = 3,248 [23]). In individuals with higher risk of exposure to ticks such as forestry and agricultural workers seroprevalences between 8% and 52% have been described [15], [18], [19], [24]–[26].", etc., etc. (http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041321 https://doi.org/10.1371/journal.pone.0041321)

Producing inaccurate data – (an inevitable result of using inaccurate tests) would predictably mislead professionals and result in the mistreatment of patients. Even if accurate seroprevalence figures could be produced, knowing how many of the population have ***antibodies*** to Lyme species bacteria, cannot inform the diagnosis or treatment of individual patients. This is exactly the same with the seroprevalance of other infections, e.g., mononucleosis, measles, etc., which does not determine the diagnosis or treatment of individual patients. Information that is genuinely 'high priority' is the ***prevalence of the infection*** in the chronically sick population, i.e., the presence of Lyme bacteria, damaging or potentially damaging tissues and leading to symptoms and illness or exacerbating other illnesses.

Coinfection

"Many patients are concerned about the possible presence of co-infections transmitted by ticks". As this concern was specifically excluded from the Scope and has not been properly addressed in the draft guideline and is represented only as a concern of 'many patients', it is safe to assume that this is not a concern of PHE or of NICE. This statement is just another stratagem to try and mollify patients. It in no way addresses the evidence, including that provided in the stakeholder responses to the Scope. E.g., Lyme Disease UK: page 53, 54, 72. Lyme Research UK: page 95, 176, 285. VIRAS: page 159, 327. Caudwell LymeCo: page 2, Lyme Disease Action: page 33 and many other references to Lyme coinfections which can cause serious complications in the effective treatment of Lyme disease and some of which represent serious diseases in their own right.

Opportunistic infections are not even mentioned by NICE, showing ignorance and/or denial of Lyme disease causing immune-suppression.

Recommendation #4

The NICE draft guideline states:

"4/ Antimicrobial management of Lyme disease

What are the most clinically and cost-effective treatment options for different clinical presentations of Lyme disease in the UK?

Why this is important

The evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme diseases is of poor quality, out-dated and often based on small studies. Most studies are not UK based. No relevant cost- effectiveness evidence was identified. A series of prospective multicentre studies is needed to compare the clinical and cost-effectiveness of different dosages and length of treatment, and the clinical and cost-effectiveness of oral compared to intravenous treatments for different presentations of Lyme disease. This is felt to be of high priority as it has enormous implications for patients and for NHS costs. There is currently insufficient quality evidence on the most effective drug and dose, and the effectiveness of extended treatment or retreatment regimens in those with continuing symptoms remains uncertain. Clarification could improve outcomes, reduce costs and may minimise unnecessary treatment."

At first glance, this research recommendation looks encouraging, but examined critically some disturbing incongruities become evident.

The draft NICE guideline provides restrictive treatment recommendations, which VIRAS believe are unfounded and unethical. NICE admit that the clinical effect of "different dosages and length of treatment" are unknown, yet at the same time they make definite and restrictive treatment recommendations which according to ther own statement - cannot be 'evidence based'. VIRAS believe this to be unfounded and unethical. The proposal for 'multicentre studies' supports our view that there is no evidence or justification for restricting treatment options for patients or doctors.

The only rationale for an expensive 'multicentre' study would be if various borrelia species produce different responses to treatment and these are expected to vary according to different regions of England and Wales. 'Multicentre' studies are not required for 'prospective' studies, they are only required for such time as a full-scale Clinical Trial is designed. This research proposition is wildly excessive and as such, it does not appear to be authentic.

As noted in the introduction, Public Heath England's Dr Matthew Dryden, claims 100% treatment success for Lyme disease. If this were true, then what possible justification could there be for spending hundreds of thousands of pounds on this research? This is bogus.

Costs and accuracy – which do you think come first?

Note how the explanation for this recommendation repeatedly mentions 'cost', except where it makes reference to 'those with continuing symptoms'. That is where cost actually matters most, because those are the patients that if still infected, will need the longest and most expensive treatment and management. Perhaps NICE overlooked this very obvious point, or perhaps it is their intention that these patients will be made 'cost-effective' even if it requires some dodgy research to make it happen. Then the most expensive patients could be re-diagnosed with some made-up illness that will not cost a penny in treatment to either the NHS or medical insurance companies, because it has no known aetiology, no treatment or ICD coding.

Establishing the UK, as a world-leader in *recommending* Lyme disease research - but not *doing* any

If these research recommendations look vaguely hopeful, please ask this question: Where do NICE imagine that the millions of pounds needed to make their research recommendations a reality, are going to come from? NICE do not fund research, and it seems that neither does anybody else in the UK.

It is notable that in the past 16 years the Medical Research Council has not allocated funding for a single study into Lyme disease. In the past 16 years, of the 7 billion pounds allocated to around 20,000 research projects of medically related research by the Wellcome Trust, only 2 projects were vaguely relevant to Lyme disease patients and doctors. One was a study of pathogens found in ticks in Europe led by the late Professor Klaus Kurtenbach which included investigation of borrelia species in ticks in the UK. The second was a study of borrelia spirochaetes in ticks in the Baltic region of Europe, led by Dr Sarah Randolph. The Cochrane library list one systematic review of Lyme disease treatment, relating to treatment of neurological complications but not focussed on the UK. The National Institute for Health Research (NIHR) list no projects for Lyme disease. However, the University of Liverpool is getting some funding from NIHR for Health Protection Research and indicate that zoonoses including Lyme: "will explore new ways of detecting and characterising pathogens". This is a drop in the ocean and cannot be expected to translate into benefit for patients or doctors in the foreseeable future.

Conclusion

As with the other research recommendations, #4 does not withstand critical examination but is revealed to be a disingenuous stratagem.

Recommendation #5

The NICE draft guideline states:

5 What are the best laboratory tests to diagnose initial and ongoing infection and determine re-infection in the different presentations of Lyme disease in the UK

> What is the most clinically and cost effective serological antibody-based test, biomarker (such as CXCL13), lymphocyte transformation and ELISPOT for diagnosing Lyme disease in the UK at all stages, including reinfection?
>
> **Why this is important**
> Determining the most clinically and cost effective diagnostic tests for Lyme disease will improve patient care and is of high priority. The clinical presentation of Lyme disease is very variable, with diagnosis of all presentations except erythema migrans relying in part on laboratory testing. Current literature suggests that a combined IgG/IgM ELISA based on the C6 peptide and immunoblot are useful but published evidence is of either low or very low quality and is not UK based. There is evidence of variation in the C6 peptide between the principal Borrelia genospecies in UK ticks and a combination of ELISAs may improve sensitivity.
>
> A 'test of cure' for Lyme disease does not exist, and, consistent with most other infectious diseases, positive serology is likely to remain positive following successful treatment of acute infection in the majority of patients. However, we know little about the evolution of antibody titres over time in those who have been treated successfully and in those who have persisting symptoms. It is frequently stated that early antibiotic treatment of Lyme disease abrogates the immune response, so that serology remains or becomes negative. The evidence base for this is minimal, and this is not a common occurrence in other infections. Understanding the natural course of Lyme disease serology and non-serological tests over time may assist in the interpretation of test results in patients who remain symptomatic and in those who are high risk for re-infection, such as those with occupational exposure.
>
> In particular, further research into the value of CXCL13 and other biomarkers including, ELISPOT testing and lymphocyte transformation tests may be helpful to support the current low quality evidence."

VIRAS appreciate the acknowledgement that NHS testing is inadequate and that improving it is 'high priority', but this statement reveals some disturbing assumptions and prejudices.

Direct detection tests are not mentioned: culture, immuno-flourescent antibody staining, including molecular beacons (the latter being 100% specific) and PCR, all of which can detect the presence of the actual infective organism – not only an immune response which NICE have already indicated can last for 3 years after treatment, making NHS tests irrelevant to a substantial number of patients at risk and useless for determining treatment failure or prevalence.

NICE state: "However, we know little about the evolution of antibody titres over time in those who have been treated successfully and in those who have persisting symptoms."

This loaded statement implies that there are only two possible outcomes to treatment: 1/ the patient is cured, or 2/ "persisting symptoms", and as already noted, NICE explain the latter as NOT treatment failure (p12 lines 1 – 10). Even though "treatment failure" is mentioned in the

draft, it is not addressed. There are no good medical or scientific justifications for this omission. The draft guideline evasion of treatment failure is unjustifiable.

'Reinfection' is mentioned but failed-treatment or delayed-relapse due to failed-treatment are not. Perhaps NICE do not want these patients to have a valid test, which could be interpreted as a strategy to discriminate against and marginalise those patients, deny them treatment and permit their ongoing infection to progress. This stratagem would permit PHE to claim that all cases of proven 'post-treatment' Lyme must represent 'reinfection'. That would give PHE a useful get-out for their years of individual and collaborative failures. They can evade blame for harms resulting from inadequate treatment because the patient must have got 'reinfected'. Therefore this serves the interests of PHE whilst discriminating against patients and their medical needs.

The claim that "diagnosis of all presentations except erythema migrans relying in part on laboratory testing", is badly misleading and reconfirms our objections that this draft guideline assumes that NHS testing for Lyme can reliably diagnose the disease and must therefore also be able to rule it out. No diagnosis of Lyme disease can 'rely' in part or whole on NHS laboratory tests. These tests can only provide support for a positive clinical diagnosis in-line with the test kit manufacturer's instructions.

How will 'cost effectiveness' be calculated? What price will NICE put on a formerly healthy person spending years or decades confined to their home due to undiagnosed, untreated or under-treated Lyme disease?

The gold-standard test for any infection is direct detection of the infective organism, which for some reason best known to themselves, NICE have omitted. The draft guideline specifies a "serological antibody-based test". This bias would allow PHE/RIPL tests to be judged only against tests with related methodologies, rather than against the best that can be achieved. This would predictably help to preserve the PHE/RIPL monopoly on UK testing. This anti-trust strategy must be eliminated. The 'customer' for NHS Lyme tests is not PHE or RIPL or doctors, it is the patients that get tested and whose health may depend on their accuracy. It is the interests of patients and what they want and need that must come first. Patients may understandably place a high value on their health. They may appreciate being able to go to work, have holidays and play an active role in their social circles. They may enjoy being able to walk, talk, read and watch TV. Those that understand that severe Lyme disease could deprive them of all of those things, might well consider that a £200 test with 60% sensitivity would be a better purchase than a £50 test with 50% sensitivity. Society at large might also agree if it understands that inaccurate testing could deprive it of thousands of formerly productive citizens, who have become disabled because of a false-saving on testing.

Conclusion to the NICE Research Recommendations

Only a fool would believe for one second that the research recommended by NICE will ever be carried out in the UK. The cost would be colossal and it would take many years. Thirty years of inaction by the public health authorities should be sufficient to convince anyone that these recommendations are pure hot-air which cost nothing to NICE or Public Health England.

The bias and assumptions which SHOULD be eliminated by bona-fide research are glaringly obvious by what is included and what is omitted from the recommendations. This cannot be put down to ignorance. These recommendations were contrived by people that knew exactly what they were doing, what the want, and what they absolutely cannot allow the public to know about Lyme disease.

If all of these projects were actually completed, the public would still not know that chronic Lyme disease is a terrible reality for tens of thousands of patients. Doctors would not know that

laboratory testing can only help in diagnosing around 50% of patients, and that is for patients that get tested within months of getting infected. Those infected for a year or longer will probably have a much smaller chance of testing positive with the tests used by the NHS, even though the infection could still be progressing and causing injury. Many patients will still not get adequate treatment and along with undiagnosed patients, thousands will still be misdiagnosed with M.E., CFS, MS, Fibromyalgia, etc., and left to rot and die in a medical limbo created by PHE and NICE.

It is clear that these issues are not about differences of ***opinion*** - because authentic scientific research aims to establish facts and should never be designed to prove one side of genuine disagreement. It can therefore be concluded that the NICE research recommendations are evidence of a biased Guideline Development Committee exploiting its power to control what they want doctors, patients and the public to believe about Lyme disease. As the product is so blatantly discriminatory, patients might at least hope that their own doctors will act based on their sensible judgement and a sincere wish to help their patients. Neither of which feature in the NICE draft guideline or its research recommendations.