LYME DISEASE INFORMATION March 25, 2015

LYME DISEASE - AN URGENT APPEAL FOR REFORM

Concerning the IDSA's preparation of new guidelines for Lyme disease

BACKGROUND

The Lyme Disease Treatment Guidelines, authored by the Infectious Diseases Society of America (IDSA), are currently undergoing review. While there are multiple perspectives regarding the best treatment protocols for Lyme disease, and two professional medical societies that specialize in the diagnosis and treatment of Lyme disease, the CDC and the nation's insurance companies have historically selected the guidelines authored by the IDSA to be the sole voice for treatment advice for this highly complex and insufficiently understood illness. This has laid the groundwork for a lack of adequate treatment for hundreds of thousands of Lyme disease patients who have endured, and will continue to endure serious, persistent illness.

In 2013, the CDC acknowledged that more than 300,000 people each year are infected with Lyme disease in the US. A significant percentage of this population does not improve with traditional treatment. The CDC estimates a range from 10% to 20%, but researchers believe the actual percentages of patients whose symptoms persist to be much higher. Developing a well-informed and comprehensive response to this growing threat is a national imperative, and one that must be executed fairly, responsibly, and without bias.

When Lyme disease emerged on the national radar in the 1970's, some researchers and physicians were confounded by the failure of patients to recover from this infection using traditional treatments. With the passing of years and the introduction of IDSA Treatment guidelines for Lyme disease in 2000, a number of physicians found the new IDSA guidelines unsatisfactory. Some patients simply did not get better. The guidelines were too restrictive and shortsighted and if followed, proved to be deleterious to the health of a frightening number of patients.

In addition, the guideline authors were possibly influenced by special interests, as demonstrated by Senator Blumenthal in 2006 when, as Attorney General of Connecticut, he filed an anti-trust suit against the IDSA. (See APPENDIX C.) Then Attorney General Blumenthal's investigation concluded that there was evidence of antitrust behavior in the creation of the IDSA guidelines and significant undisclosed conflicts of interest in the majority of members of the Guidelines review panel. The suit required that the IDSA create a new "review panel" to re-review the then current guidelines. Unfortunately, this new panel had only IDSA followers as members, likely influencing them, in a self-dealing manner, that there were no problems with their own guidelines. Our well founded concern is that this current IDSA panel will rely only on their own expert opinion (as the 2008 panel and prior review panels had) and will ignore the body of scientific evidence, which in effect, points to the medical necessity of more comprehensive, less restrictive treatments.

In particular, research and experience has shown that the IDSA may be incorrect in their steadfast denial of the possibility that "persistent" disease is a **feature** of the infection, in light of the fact that strict adherence to the IDSA guidelines has resulted in long term suffering in tens of thousands of patients -- suffering which perhaps could have been avoided with a more comprehensive treatment approach.

Over the past 30 years, a body of independent research and clinical experience has been compiled; it offers compelling evidence that challenges many of the long-held IDSA tenets and at the very least, according to the Institute of Medicine's Standards for creating guidelines, new evidence warrants inclusion and not dismissal. Indeed, the IDSA has continued to dismiss this body of evidence. The new

evidence contradicts a number of conclusions of IDSA research and therefore, should be of great concern to the US Congress. By failing to include the full scope of available science, the IDSA has not been able to develop one useful, comprehensive set of guidelines. This, according to patients across the country and around the world, has been devastating for them. Currently, as thousands will testify, there are medical professionals who bravely go outside the restrictive IDSA guideline box in order to save their patients.

Great scientific uncertainty regarding proper diagnosis and testing exists. This uncertainty further complicates the formation of one final set of treatment guidelines. Medical ethics dictate that when test results have been proven to be inaccurate and multiple treatment options exist, then, if a diagnosis is determined, patients should be informed about ALL treatment options and be given the right to choose a treatment protocol. Yet, in the case of Lyme disease, the IDSA, and by extension, the medical community at large, ignores this mandate, and only endorses the IDSA Guidelines. This "selection bias" also exists despite a CDC survey that reported persisting symptoms in patients who received a short-term course of antibiotic treatment (*see APPENDIX A*), can lead to long-term disability. In spite of these compelling factors, since 2000, IDSA Guidelines have been continually favored, thereby denying the medical community and the American public access to other medically recognized perspectives regarding treatment.

It is essential that the process by which all guidelines are reviewed and adopted be careful to not only follow IOM Standards, but to ensure the best result so that the best options will be available to all patients.

THE REVIEW PROCESS NOW UNDERWAY

As recommended by the Institutes of Medicine, organizations are advised to review and appropriately revise their Treatment Guidelines to reflect new science every five years.

The IDSA has notified the public that their Lyme Disease Treatment Guidelines are under review, and a 30-day comment period, that precedes the release of the Guidelines, will expire on April 9, 2015. This of course, is in the best interest of the health of American citizens.

The public and scientists and physicians who have reviewed the IDSA review process find troubling indications that the IOM's Standard's are not being observed. The following would indicate that this process is likely being manipulated to result in Guidelines that serve the competitive interests of the Infectious Diseases Society of America and its influential senior members, rather than the American public. Items of specific concern include:

1. There is no one on the IDSA Review panel representing the research conducted in the past ten years that supports the theory that the causative agent of Lyme disease, Borrelia burgdorferi, can persist after antibiotic therapy, thus possibly accounting for the failure of a percentage of patients to recover. (See APPENDIX B for specific studies and references.)

2. In violation of IOM Standards, the panel does not include representatives from key affected groups, including a current or former patient and a patient advocate or patient organization representative. Indeed, the single "Consumer Representative" chosen to represent the interests of patients suffering with Lyme disease is from Nebraska, a non-endemic region and she has no familiarity with Lyme disease. Thousands of patients want to express their concerns regarding the limits of the IDSA Guidelines and it is important that their voices be heard.

3. Contrary to the Institute of Medicine "Standards for Developing Trustworthy Clinical Practice Guidelines," a number of members on the current IDSA guidelines panel have known conflicts of interest. (Please see Appendix D)

To ensure a fair process, the following research should be reviewed and properly represented during the IDSA review. Please return confirmation of said review to the address above:

- Bradley JF,et al, The Persistence of Spirochetal Nucleic Acids in Active Lyme Arthritis. Ann Int Med 1994;487-9
- Bayer ME, Zhang L, Bayer MH. Borrelia burgdorferi DNA in the urine of treated patients with chronic Lyme Disease symptoms. A PCR study of 97 cases. Infection 1996. Sept-Oct;24(5):347-53
- Diringer MN, et al, Lyme meningoencephalitis- report of a severe, penicillin resistant case. Arthritis & Rheum, 1987;30:705-708
- Donta, ST, Tetracycline therapy in chronic Lyme disease. Chronic Infectious Diseases, 1997; 25 (Suppl 1): 552-56
- Fitzpatrick JE, et al. Chronic septic arthritis caused by Borrelia burgdorferi. Clin Ortho 1993 Dec;(297):238-41
- Georgilis K, Peacocke M, &Klempner MS. Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. J Infect Dis 1992;166: 440-444
- Fallon BA, et al. Repeated antibiotic treatment in chronic Lyme disease, Journal of Spirochetal and Tick-borne Diseases, 1999; 6 (Fall/Winter):94-101
- Fraser DD, et al. Molecular detection of persistent Borrelia burgdorferi in a man with dermatomyositis. Clinical and Exper Rheum. 1992;10:387-390
- Fried MD et al, Borrelia burdorferi persists in the gastrointestinal tract of children and adolescents with Lyme Disease, JNL of Spirochetal and Tick-borne Diseases, Spring/Summer 2002; 9:11-15
- Girschick HJ, et al. Intracellular persistence of Borrelia burgdorferi in human synovial cells. RheumatolInt 1996;16(3):125-132
- Hassler D, et al. Pulsed high-dose cefotaxime therapy in refractory Lyme Borreliosis (letter). Lancet 1991;338:193
- Horowitz RI. Chronic Persistent Lyme Borreliosis: PCR evidence of chronic infection despite extended antibiotic therapy: A Retrospective Review. Abstract XIII Intl Sci Conf on Lyme Disease. Mar 24-26, 2000.
- Haupl T, et al. Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum 1993;36:1621-1626
- Karma A, et al. Long term follow-up of chronic Lyme neuroretinitis. Retina 1996;16:505-509
- Keller TL, et al. PCR detection of Borrelia burgdorferi DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. Neurology 1992;43:32-42
- Masters EJ, et al. Spirochetemia after continuous high-dose oral amoxicillin therapy. Infect DisClin Practice 1994;3:207-208
- Ma Y, et al. Intracellular localization of Borrelia burgdorferi within human endothelial cells. Infect Immun 1991;59:671-678
- Meier P, et al. Pars planavitrectomy in Borrelia burgdorferiendophthalmitis. KlinMonatsblAugenheilkd 1998 Dec;213(6):351-4
- Preac-Mursic V, et al. Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection 1989;17:355-359.
- Preac-Mursic V, et al. Persistence of Borrelia burdorferi and Histopathological Alterations in Experimentally Infected Animals. A comparison with Histopathological Findings in Human Lyme Disease. Infection 1990;18(6):332-341
- Straubinger RK, et al. Persistence of Borrelia burgdorferi in Experimentally Infected Dogs after Antibiotic Treatment. J ClinMicrobiol 1997;35(1):111-116
- Embers, M. et al. Persistence of Borrelia burgdorferi in Rhesus Macaques following Antibiotic treatment of Disseminated Infection. PLoS ONE 7(1): e29914. doi:10.1371/journal.pone

Chronic persistent infection with Bb despite intensive antibiotics was also proven in two recent Xenodiagnostics studies. The first was in mice:

- Hodzic E, Barthold SW (2014) Resurgence of Persisting Non-Cultivable Borrelia burgdorferi following Antibiotic Treatment in Mice. PLoS ONE 9(1): e86907.

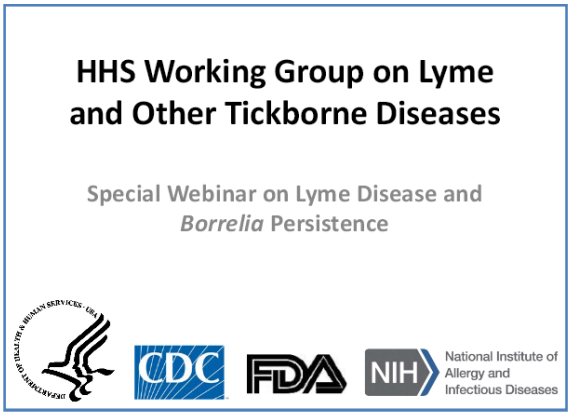
Results confirmed previous studies: Bb could not be cultured from tissues, but low copy numbers of Bb flaB DNA were detectable in tissues up to 8 months after completion of treatment & RNA transcription of genes was seen with visualized spirochetes.

In humans, a recent NIH study by Dr Marques showed that among ten patients who had high levels of antibodies against B. burgdorferi after antibiotic treatment, two of those patients had "indeterminate results", and one patient with Post Treatment Lyme disease syndrome (PTLDS) had a positive result, confirming evidence of ongoing Borrelia DNA in these patients:

- Marques, A. et al. Xenodiagnosis to Detect Borrelia burgdorferi Infection: A First-in-Human Study. Clinical Infectious Diseases DOI: 10.1093/cid/cit939 (2014).
- Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines,DongHeun Lee, MD; Ole Vielemeyer, MD; Arch Intern Med. 2011;171(1):18-22
- (Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the United States. Infection 1996 Mar-Apr;24(2):182-6).
- Hook S, Nelson C, Mead P. Self-reported Lyme disease diagnosis, treatment, and recovery: Results from 2009, 2011, & 2012 Health Styles nationwide surveys. Presented at The 13th International Conference on Lyme Borreliosis and other Tick Borne Diseases, Boston, MA Aug 19, 2013. Available from: http://archive.poughkeepsiejournal.com/assets/pdf/BK211780914.pdf.
- Marangoni, A. et al. Comparative evaluation of three different ELISA methods for the diagnosis of early culture-confirmed Lyme disease in Italy. J. Med. Microbiol. 54, 361-367 (2005);
- Ang, C.W.,et al. T. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. Eur. J. Clin. Microbiol. Infect. Dis. 30, 1027-1032 (2011).
- Wojciechowska-Koszko, et al. Serodiagnosis of borreliosis; Arch. Immunol. Ther. Exp. 59, 69-77 (2011).
- (Coulter,etal.,J Clin Microbiol 2005;43:5080-5084
- Aucott JN, et al. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: is there something here? Qual Life Res. 2013 Feb;22(1):75-84
- Centers for Disease Control Prevention MMWR56(23);573-576, June 15, 2007 http://www.cdc.gov/ncphi/disss/nndss/casedef/lyme_disease_2008.htm
- Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y Follow-up study of patients with neuroborreliosis. Scand J Infec Dis. 2002;34(6):421-5.
- Valesová H, Mailer J, Havlík J, Hulínská D, Hercogová J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. Infection. 1996 Jan-Feb;24(1):98-102
- Logigian (1990) : After 6 mo's of therapy, 10/27 patients treated with IV antibiotics relapsed or had treatment failure.
- Pfister (1991): 33 patients with neuroborreliosis were treated with IV antibiotics, and after a mean of 8.1 months 10/27 were symptomatic and borrelia persisted in the CSF in 1 patient.
- Shadick (1994) : 10/38 pts relapsed (5 with IV) within 1 year of treatment, and had repeated antibiotic treatment.
- Asch (1994) : 28% relapsed w/ major organ involvement 3.2 years after initial treatment
- Antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. The New England journal of medicine. 2001 Jul 12:85-92
- Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30
- Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008 Mar 25:992-1003
- Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Review Anti-Infective Therapy. 2014 Sep;12(9):1103-35.
- Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011. Available from: http://books.nap.edu/openbook.php?record_id=1305
- Fallon BA, Petkova E, Keilp J, Britton C. A reappraisal of the U.S. clinical trials of Post-Treatment Lyme Disease Syndrome. Open Neurology Journal. 2012;6(Supp. 1-M2):79-87.

- Liegner KB. Lyme Disease: The Sensible Pursuit of Answers.(Guest Commentary). J ClinMicrobiol 1993;31:1961-1963.
- Liegner KB, Shapiro JR, Ramsay D, Halperin AJ, Hogrefe W, Kong L. Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting Borrelia burgdorferi Infection. J AmerAcadDerm 1993;28:312-4.
- Liegner KB, Duray P, Agricola M, Rosenkilde C, Yannuzzi L, Ziska M, Tilton R, Hulinska D, Hubbard J, Fallon B. Lyme Disease and the Clinical Spectrum of Antibiotic-Responsive Chronic Meningoencephalomyelitides. J Spirochetal and Tick-borne Dis 1997;4:61-73.
- Fallon BA, Tager F, Fein L, Liegner K, Keilp J, Weiss N, Liebowitz MR. Repeated Antibiotic Treatment in Chronic Lyme Disease. J Spirochetal and Tick-borne Dis 1999;6:94-102.
- Delong et al. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: A biostatistical review of randomized, placebo controlled, clinical trials. Contemporary Clinical Trials 33 (2012), 1132-1142
- Wahlberg,P. et al, Treatment of late Lyme borreliosis. J Infect, 1994. 29(3): p255-61 →31% improved w/ 14 days of Rocephin, 89% improved w/ Rocephin + 100d of Amoxicillin and Probenecid, 83% improved w/ Rocephin, then 100 days of cephadroxil
- Donta, ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6. →277 pts with chronic LD treated between 1-11 months: 20% cured, 70% improved, 10% failed
- Oksi, J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J ClinMicrobiol Infect Dis, 1998. 17(10) :p 715-9→ 30 pts w/ chronic Lyme disease were treated for 100 days, and 90% had good or excellent responses
- Oksi, J., et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med, 1999. 31(3):p.225-32→32/165 patients with disseminated Lyme were treated for 1 or more months of antibiotics, and showed that even more than 3 months of treatment may not eradicate the spirochete, and that longer term therapy may be necessary.

Additional Resources
APPENDIX A



Summary of HHS Special Webinar of Lyme Disease and Borrelia Persistence, May 22, 2014
Convened by Dr. Ben Beard, CDC, NCEZID, Div. of Vector-borne diseases
Moderated by Dr. Joseph Breen, NIH, NIAID

Stated Purpose of Webinar: To discuss the state of the science with regard to persistence of infection by *Borrelia burgdorferi* (the bacterial agent that causes Lyme disease).

As expressed by Dr. Ben Beard in his opening comments of this webinar, the official position of the Centers for Disease Control with regard to the treatment of Lyme disease, a bacterial infection

transmitted by ticks, is that 2 to 4 weeks of oral doxycycline results in a "symptomatic cure" for the "great majority" of Lyme disease patients. However, the results of a CDC Health Survey presented in poster session at the *International Conference of Lyme Borreliosis and Other Tick-borne Diseases* by Dr. Paul Mead et. al. of the CDC in August 2013 showed that approximately 1% of survey respondents (n=3503) had been diagnosed with Lyme disease in the United States in 2012, which resulted in the CDC revising estimates of the number of cases of Lyme disease upward by a factor of 10, to approximately 312,000 cases of Lyme disease annually. This CDC survey also showed that of those who had been diagnosed, 61% were treated with antibiotics for longer than the recommended 2 to 4 weeks, and that one-third of the respondents did not experience a "symptomatic cure" of their symptoms after 6 to 24 months. Patients who continue to have symptoms of Lyme disease after antibiotic treatment that may last for months to years are characterized as having "Post-treatment Lyme Disease Syndrome" by the CDC and NIH. This is also referred to as "chronic" Lyme disease, implying that symptoms do not resolve following antibiotic treatment due to the biological capacity of *Borrelia burgdorferi*, a spirochete bacterium, to survive the antibiotic treatment and cause persisting infection.

There are three hypotheses to explain why a significant number of people with Lyme disease do not experience a symptomatic cure of their symptoms when treated with 2 to 4 weeks of oral doxycycline. These are (1) induction of an inflammatory response by dead spirochetes or cell parts remaining after antibiotic treatment; (2) continuation of an active infection by live spirochetes that survive the antibiotic treatment; or (3) an "autoimmune" series of irreversible sequelae from a previous infection. Persistence of *Borrelia* spp. in animals or humans following antibiotic treatment is strong evidence that unresolved symptoms are due to continuation of an active infection.

To briefly summarize the proceedings of the HHS Special Webinar on Lyme disease and *Borrelia* Persistence, **there is consensus that *Borrelia* spp. can cause persistent infection in several animal hosts and in humans**. Specifically, the scientific evidence includes the findings that *Borrelia* DNA, RNA, proteins, and culturable spirochetes can be recovered from infected animals that have been treated with antibiotics (with the concomitant observation that DNA alone rapidly becomes undetectable when injected into host animals); that *Borrelia* DNA can be recovered from humans with PTLDS; and that studies with human subjects are needed. Human studies will require the development of better methods of testing for correlating infection with persistence of symptoms in humans.

Public and non-public scientists were convened for this webinar. The following is a summary of the individual presentations from the transcript of the webinar available at the CDC website.

Dr. Stephen Barthold, University of California, Davis

- The life cycle of *Borrelia* spp. is complex and includes multiple reservoir hosts and three life stages of ticks, which would not be biologically possible if persistent infection was not part of this life cycle.
- Persisting infection has been confirmed in studies involving humans who are not treated with antibiotics.
- *Borrelia* DNA and RNA transcripts of *Borrelia* genes, which indicates biological activity by live bacteria, are found in infected animals (mice, rats, hamsters, guinea pigs, gerbils, dogs, and 2 species of non-human primates) after antibiotic treatment.
- DNA alone, when injected into animals (or fetal DNA in the maternal circulation) is rapidly cleared and becomes undetectable.
- Pro-inflammatory cytokine responses are seen in persistently-infected animal models.

Dr. Linda Bockenstedt, Yale University School of Medicine

- Spirochetes are difficult to grow in culture under normal circumstance, which is why culture-based methods to detect *Borrelia* or diagnose Lyme disease are not used for human diagnostics.

- Using xenodiagnostic methods, viable spirochetes (as determined by culture) and *Borrelia* DNA was found in infected, antibiotic-treated mice in one mouse model (B6), but not in C3H mice, in which "remnants" of spirochetes, which were not culturable but that contained DNA, were observed. These results are contradictory, and indicate that genetic variation in the host may influence the course of the disease and the extent of the disease symptomsin mice.
- Persisting symptoms may be due to either continuing active infection by live spirochetes, or may be due to inflammation triggered by *Borrelia* "remnants" in tissues.
- Persistence of symptoms after antibiotic treatment in humans needs to be studied in a human system, in the context of the emerging research on the human microbiome (bacteria that live in/on humans and play an active role in both health and disease).

Dr. Monica Embers, Tulane University

- Rhesus macaque monkeys (non-human primates) are a good model system for Lyme disease because the disease course is very close to what is seen in humans.
- Numerous studies have previously shown that *Borrelia* may evade the human/animal immune response, that the bacteria can survive for months to years in ticks without nutrient replenishment and without reproducing, and that they are found deep in connective tissues, which are sites not readily penetrated by most antibiotics.
- Culturable spirochetes (and *Borrelia* DNA) are recovered from infected monkeys following treatment with doxycycline at concentrations that far exceed human dosage.

Dr. Adriana Marques, NIAID

- Xenodiagnosis using laboratory-raised ticks is safe as a method of study in humans.
- Ticks applied to humans with various forms of Lyme disease were tested for spirochetes or *Borrelia* DNA by culture, PCR, and by mass spectrometry.
- Ticks that fed on the "positive control," which was a person with known early Lyme disease and taking doxycycline at the time of the study, had DNA from two different genotypes of *Borrelia burgdorferi*.
- 1 of 10 people in the PTLDS (Post-treatment Lyme Disease Syndrome) group was positive for *Borrelia* by mass spectrometry, and the bacterium was found to be a "novel" genotype by DNA analysis. This person was again positive for the same genotype of Borrelia in a separate xenodiagnosis procedure 8 months later.
- 2 additional people in the PTLDS group were positive for *Borrelia* by mass spectrometry, but the recovered DNA was similar to the DNA of a reference (laboratory) strain of *Borrelia*, so these were not considered "positive."
- A "possible hypothesis" to explain the recovery of *Borrelia* from 1 to 3 (of 10) PTLDS patient(s) is continuing active infection by the spirochetes in the people with PTLDS.

Dr. Linden Hu, Tufts University

- There are several findings with regard to *Borrelia* infection that are consistent across labs (meaning, there is consensus on the following):
    - Antibiotic treatment decreases the number of bacteria and/or levels of DNA.
    - Antibody levels decrease in animals after antibiotic treatment.
    - DNA, RNA, and proteins from *Borrelia* can be detected in animals after antibiotic treatment; however, spirochetes can't be "cultured" from antibiotic-treated animals. Possible explanations for this include persistence of the DNA, RNA or protein molecules as remnants of the infection after the bacteria are dead, or that the bacteria are alive but "altered" by the antibiotics so that they are no longer culturable.

- The latter hypothesis (that antibiotics alter the bacterial phenotype) is supported by many studies on bacteria that show a "persister" state after antibiotics. *Coxiellaburnetii* (causative agent of Q fever) is one example of a bacterium that causes long term disease treated with long term antibiotics, for which DNA and bacterial proteins are found to persist in infected hosts. Transplanted tissues from infected hosts can transfer those bacterial antigens to a new host, but the bacteria cannot be cultured from the new host.
- Antibiotics are an agent of natural selection, and antibiotic treatment selects for the phenotype of non-replicating "persister" cells.
- "*Borrelia* does not break the rules (of infection), we just don't understand the rules"

The research described in this webinar, together with the data from the Health Surveys conducted by the CDC indicating that the number of Lyme disease cases is 6 times greater than the number of cases of HIV/AIDS on an annual basis, illustrate the need for a broader review of the science pertaining to Lyme disease in the United States.

This summation was compiled by Holly Ahern, Associate Professor of Microbiology, SUNY Adirondack (ahernh@sunyacc.edu)

APPENDIX B

ADDITIONAL COMMENTS AND CITATIONS

1. Physicians in the United States have a choice to follow either of these two evidence based guidelines, but there are known problems with the IDSA guidelines. A published scientific review in the **Archives of Internal Medicine that-**analyzed the overall level of evidence behind the IDSA guidelines concluded:

   "We analyzed the strength of recommendation and overall quality of evidence behind 41 IDSA guidelines released between January 1994 and May 2010…More than half of the current recommendations of the IDSA are based on level III evidence only (opinion). Until more data from well-designed controlled clinical trials become available, physicians should remain cautious when using current guidelines as the sole source guiding patient care decisions".

   Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines,DongHeun Lee, MD; Ole Vielemeyer, MD; Arch Intern Med. 2011;171(1):18-22

2. The majority of physicians in the United States in fact do not follow IDSA guidelines. They treat for seronegative disease, and treat for extended periods of time. An article published in the journal Infection in 1996 by Dr. Sam Donta highlighted the discrepancy, and showed that the majority of physicians do not treat according to IDSA guidelines:

   "For chronic Lyme disease, 57% of responders treat 3 months or more."

   (Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the United States. Infection 1996 Mar-Apr;24(2):182-6).

3. A recent study by the CDC confirmed the same data. The CDC surveyed a representative sample of people in the US and found that only 39% of those with Lyme disease were treated in accordance with blanket short term recommendations in the IDSA guidelines. The majority were treated for longer periods.

   Hook S, Nelson C, Mead P. Self-reported Lyme disease diagnosis, treatment, and recovery: Results from 2009, 2011, & 2012 Health Styles nationwide surveys. Presented at The 13th

International Conference on Lyme Borreliosis and other Tick Borne Diseases, Boston, MA Aug 19, 2013. Available from: http://archive.poughkeepsiejournal.com/assets/pdf/BK211780914.pdf.

4. The reason the majority of physicians in the United States do not follow IDSA guidelines is because more than half of their recommendations are based on poor scientific evidence (known as level III evidence) and it has been demonstrated that the two-tier testing approach recommended by the IDSA often does not work in clinical practice. According to these guidelines, a Western blot is not to be performed if the ELISA is negative, despite the poor sensitivity of ELISA tests ranging from 34% to 70.5%. The effect of using the IDSA guidelines would be to miss roughly half of those suffering with Lyme disease.
   - Marangoni, A. et al. Comparative evaluation of three different ELISA methods for the diagnosis of early culture-confirmed Lyme disease in Italy. J. Med. Microbiol. 54, 361-367 (2005);
   - Ang, C.W.,et al. T. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. Eur. J. Clin. Microbiol. Infect. Dis. 30, 1027-1032 (2011).
   - Wojciechowska-Koszko, et al. Serodiagnosis of borreliosis; Arch. Immunol. Ther. Exp. 59, 69-77 (2011).

5. John Hopkins University also found problems with the CDC two-tiered testing approach. In 2005, John's Hopkins did a study and found that the CDC two-tiered testing missed up to 55% of positive Lyme cases.
   (Coulter,etal.,J Clin Microbiol 2005;43:5080-5084).

6. A NYS DOH study done in 1996 that was reported to the CDC, found the number of patients missed by the two-tiered protocol (without an EM rash) to be even higher: 81% of Non-EM Cases were not confirmed with present two-tiered testing algorithms (CDC correspondence with NYS DOH, April 15th, 1996).

Inaccurate diagnostic tests, based on technology that is over 20 years old, creates medical uncertainty in both the diagnosis and treatment of Lyme disease

7. In 2013, the CDC acknowledged that more than 300,000 people a year will be infected with Lyme disease in the US. They estimate that 10% to 20% of this population will suffer long-term illness as a result of their Lyme infection. (Many researchers believe this estimate to be very low.) (http://www.cdc.gov/lyme/treatment/).

   Other studies suggest the treatment failure rate for early Lyme disease may be as high as 36%:
   Aucott JN, et al. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: is there something here? Qual Life Res. 2013 Feb;22(1):75-84

   In late Lyme disease, treatment failure rates may exceed 50%:
   Cameron, D., Horowitz, R, et al: Treatment of Lyme disease: a medicolegal assessment. Expert review of anti-infective therapy. 2004 Aug;2(4):533-57

8. Lyme disease is the number one vector borne spreading infectious disease in the US, and it is first and foremost, a clinical diagnosis. Blood tests are known to be unreliable, and the two-tiered approach put forth by the IDSA is only intended to be used by health departments to epidemiologically screen large populations for the disease. This was highlighted years ago on the CDC web site. In the words of the CDC:

"This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis."

Centers for Disease Control Prevention MMWR56(23);573-576, June 15, 2007
http://www.cdc.gov/ncphi/disss/nndss/casedef/lyme_disease_2008.htm

9. Prior IDSA guidelines used the CDC definition to diagnose Lyme disease, resulting in large numbers of individuals becoming chronically ill and increasing suffering and disability. Updated research on the insensitivity of testing must be included in the new guidelines, to ensure the safety of the American people.

10. Research, including recent studies, has also shown persistence of the Lyme disease bacteria despite short courses of antibiotic therapies. Insurance companies have denied appropriate care to patients, using the IDSA guidelines as their sole source for diagnosis and treatment. In order to protect the American public from this emerging epidemic, it is important that the IDSA panel comments on this substantial and compelling body of research listed below which shows chronic persistent infection despite intensive antibiotics:

- Bradley JF ,et al, The Persistence of Spirochetal Nucleic Acids in Active Lyme Arthritis. Ann Int Med 1994;487-9
- Bayer ME, Zhang L, Bayer MH. Borrelia burgdorferi DNA in the urine of treated patients with chronic Lyme Disease symptoms. A PCR study of 97 cases. Infection 1996. Sept-Oct;24(5):347-53
- Diringer MN, et al, Lyme meningoencephalitis- report of a severe, penicillin resistant case. Arthritis & Rheum, 1987;30:705-708
- Donta, ST, Tetracycline therapy in chronic Lyme disease. Chronic Infectious Diseases, 1997; 25 (Suppl 1): 552-56
- Fitzpatrick JE, et al. Chronic septic arthritis caused by Borrelia burgdorferi. Clin Ortho 1993 Dec;(297):238-41
- Georgilis K, Peacocke M, &Klempner MS. Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. J Infect Dis 1992;166: 440-444
- Fallon BA, et al. Repeated antibiotic treatment in chronic Lyme disease, Journal of Spirochetal and Tick-borne Diseases, 1999; 6 (Fall/Winter):94-101
- Fraser DD, et al. Molecular detection of persistent Borrelia burgdorferi in a man with dermatomyositis. Clinical and Exper Rheum. 1992;10:387-390
- Fried MD et al, Borrelia burdorferi persists in the gastrointestinal tract of children and adolescents with Lyme Disease, JNL of Spirochetal and Tick-borne Diseases, Spring/Summer 2002; 9:11-15
- Girschick HJ, et al. Intracellular persistence of Borrelia burgdorferi in human synovial cells. RheumatolInt 1996;16(3):125-132
- Hassler D, et al. Pulsed high-dose cefotaxime therapy in refractory Lyme Borreliosis (letter). Lancet 1991;338:193
- Horowitz RI. Chronic Persistent Lyme Borreliosis: PCR evidence of chronic infection despite extended antibiotic therapy: A Retrospective Review. Abstract XIII Intl Sci Conf on Lyme Disease. Mar 24-26, 2000.
- Haupl T, et al. Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum 1993;36:1621-1626
- Karma A, et al. Long term follow-up of chronic Lyme neuroretinitis. Retina 1996;16:505-509
- Keller TL, et al. PCR detection of Borrelia burgdorferi DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. Neurology 1992;43:32-42
- Masters EJ, et al. Spirochetemia after continuous high-dose oral amoxicillin therapy. Infect DisClin Practice 1994;3:207-208
- Ma Y, et al. Intracellular localization of Borrelia burgdorferi within human endothelial cells. Infect Immun 1991;59:671-678
- Meier P, et al. Pars planavitrectomy in Borrelia burgdorferiendophthalmitis. KlinMonatsblAugenheilkd 1998 Dec;213(6):351-4
- Preac-Mursic V, et al. Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection 1989;17:355-359.

- Preac-Mursic V, et al. Persistence of Borrelia burdorferi and Histopathological Alterations in Experimentally Infected Animals. A comparison with Histopathological Findings in Human Lyme Disease. Infection 1990;18(6):332-341
- Straubinger RK, et al. Persistence of Borrelia burgdorferi in Experimentally Infected Dogs after Antibiotic Treatment. J ClinMicrobiol 1997;35(1):111-116
- Embers, M. et al. Persistence of Borrelia burgdorferi in Rhesus Macaques following Antibiotic treatment of Disseminated Infection. PLoS ONE 7(1): e29914. doi:10.1371/journal.pone

Chronic persistent infection with Bb despite intensive antibiotics was also proven in recent Xenodiagnosticsstudies. The first study was in mice:

- Hodzic E, Barthold SW (2014) Resurgence of Persisting Non-Cultivable Borrelia burgdorferi following Antibiotic Treatment in Mice. PLoS ONE 9(1): e86907.

Results confirmed previous studies: Bb could not be cultured from tissues, but low copy numbers of Bb flaB DNA were detectable in tissues up to 8 months after completion of treatment & RNA transcription of genes was seen with visualized spirochetes.

In humans, a recent NIH study by Dr. Marques showed that among ten patients who had high levels of antibodies against B. burgdorferi after antibiotic treatment, two of those patients had "indeterminate results", and one patient with Post Treatment Lyme disease syndrome (PTLDS) had a positive result, confirming evidence of ongoing Borrelia DNA in these patients:

- Marques, A. et al. Xenodiagnosis to Detect Borrelia burgdorferi Infection: A First-in-Human Study. Clinical Infectious Diseases DOI: 10.1093/cid/cit939 (2014).
- Liegner KB. Lyme Disease: The Sensible Pursuit of Answers.(Guest Commentary). J ClinMicrobiol 1993;31:1961-1963.
- Liegner KB, Shapiro JR, Ramsay D, Halperin AJ, Hogrefe W, Kong L. Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting Borrelia burgdorferi infection. J AmerAcadDerm 1993;28:312-4.
- Liegner KB, Duray P, Agricola M, Rosenkilde C, Yannuzzi L, Ziska M, Tilton R, Hulinska D, Hubbard J, Fallon B. Lyme Disease and the Clinical Spectrum of Antibiotic-Responsive Chronic Meningoencephalomyelitides. J Spirochetal and Tick-borne Dis 1997;4:61-73.
- Fallon BA, Tager F, Fein L, Liegner K, Keilp J, Weiss N, Liebowitz MR. Repeated Antibiotic Treatment in Chronic Lyme Disease. J Spirochetal and Tick-borne Dis 1999;6:94-102.

11. Some physicians feel that there is no evidence of prolonged antibiotics helping symptoms. It is known that short term antibiotics fail in 25% to 71% of patients with late stage disease:
    - Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y Follow-up study of patients with neuroborreliosis. Scand J Infec Dis. 2002;34(6):421-5.
    - Valesová H, Mailer J, Havlík J, Hulínská D, Hercogová J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. Infection. 1996 Jan-Feb;24(1):98-102

12. These frequent treatment relapses and failures with short term therapy are documented by other authors:
    - Logigian (1990) : After 6 mo's of therapy, 10 of 27 patients treated with IV antibiotics relapsed or had treatment failure.
    - Pfister (1991): 33 patients with neuroborreliosis were treated with IV antibiotics, and after a mean of 8.1 months 10 of 27 were symptomatic and borrelia persisted in the CSF in 1 patient.
    - Shadick (1994) : 10 of 38 pts relapsed (5 with IV) within 1 year of treatment, and had repeated antibiotic treatment.
    - Asch (1994) : 28% relapsed w/ major organ involvement 3.2 years after initial treatment

13. Many doctors use IDSA guidelines to base their conclusions to avoid treating sick patients with long term antibiotics. However, only three NIH-funded trials have been conducted on the treatment of chronic Lyme disease:
    - Antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. The New England journal of medicine. 2001 Jul 12:85-92

- Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30
- Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008 Mar 25:992-1003

14. These were inadequate treatment trials as sample sizes were extremely small, ranging from 37 to 78 patients. Critics have pointed out that studies this small lack sufficient statistical power to measure clinically relevant improvement:
    - Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Review Anti-Infective Therapy. 2014 Sep;12(9):1103-35.
    - Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011. Available from: http://books.nap.edu/openbook.php?record_id=1305

15. Nevertheless, two of the three clinical trials demonstrated that retreatment improved some patients' measures, such as fatigue and pain (Krupp, Fallon). Others have shown improvement in cognitive function, in those with Lyme encephalopathy (Fallon).
    - Fallon BA, Petkova E, Keilp J, Britton C. A reappraisal of the U.S. clinical trials of Post-Treatment Lyme Disease Syndrome. Open Neurology Journal. 2012;6(Supp. 1-M2):79-87.
    - Delong et al. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: A biostatistical review of randomized, placebo controlled, clinical trials. Contemporary Clinical Trials 33 (2012), 1132-1142

The medical literature does, in fact, show a benefit to using longer treatment regimens for disseminated Lyme disease:

- Wahlberg,P. et al, Treatment of late Lyme borreliosis. J Infect, 1994. 29(3): p255-61 →31% improved w/ 14 days of Rocephin, 89% improved w/ Rocephin + 100d of Amoxicillin and Probenecid, 83% improved w/ Rocephin, then 100 days of cephadroxil
- Donta, ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6. →277 pts with chronic LD treated between 1-11 months: 20% cured, 70% improved, 10% failed
- Oksi, J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J ClinMicrobiol Infect Dis, 1998. 17(10) :p 715-9→ 30 pts w/ chronic Lyme disease were treated for 100 days, and 90% had good or excellent responses
- Oksi, J., et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med, 1999. 31(3):p.225-32→32/165 patients with disseminated Lyme were treated for 1 or more months of antibiotics, and showed that even more than 3 months of treatment may not eradicate the spirochete, and that longer term therapy may be necessary. ***This last study detected chronic persistent Lyme by both PCR and culture, the "gold standard" for proving chronic infection.**

16. "HHS/CDC/NIH/FDA SPECIAL WEBINAR - LYME DISEASE AND BORRELIA PERSISTENCE. MAY 22, 2014"
(See APPENDIX A)

In conclusion, the scientific literature shows:

- **unreliable blood tests,**
- **persistence of *Borreila* despite short term treatment,**
- **and peer reviewed clinical trials showing benefit of longer term antibiotic therapies.**

It is therefore incumbent on physicians to use their best clinical judgment in treating their patients and this substantial body evidence should be included in the IDSA review.

APPENDIX C

Connecticut Attorney General's Office Press Release

Attorney General's Investigation Reveals Flawed Lyme Disease Guideline Process, IDSA Agrees To Reassess Guidelines, Install Independent Arbiter

May 1, 2008

Attorney General Richard Blumenthal today announced that his antitrust investigation has uncovered serious flaws in the Infectious Diseases Society of America's (IDSA) process for writing its 2006 Lyme disease guidelines and the IDSA has agreed to reassess them with the assistance of an outside arbiter.

The IDSA guidelines have sweeping and significant impacts on Lyme disease medical care. They are commonly applied by insurance companies in restricting coverage for long-term antibiotic treatment or other medical care and also strongly influence physician treatment decisions.

Insurance companies have denied coverage for long-term antibiotic treatment relying on these guidelines as justification. The guidelines are also widely cited for conclusions that chronic Lyme disease is nonexistent.

"This agreement vindicates my investigation -- finding undisclosed financial interests and forcing a reassessment of IDSA guidelines," Blumenthal said. "My office uncovered undisclosed financial interests held by several of the most powerful IDSA panelists. The IDSA's guideline panel improperly ignored or minimized consideration of alternative medical opinion and evidence regarding chronic Lyme disease, potentially raising serious questions about whether the recommendations reflected all relevant science.

"The IDSA's Lyme guideline process lacked important procedural safeguards requiring complete reevaluation of the 2006 Lyme disease guidelines -- in effect a comprehensive reassessment through a new panel. The new panel will accept and analyze all evidence, including divergent opinion. An independent neutral ombudsman -- expert in medical ethics and conflicts of interest, selected by both the IDSA and my office -- will assess the new panel for conflicts of interests and ensure its integrity."

Blumenthal's findings include the following:

- The IDSA failed to conduct a conflicts of interest review for any of the panelists prior to their appointment to the 2006 Lyme disease guideline panel;
- Subsequent disclosures demonstrate that several of the 2006 Lyme disease panelists had conflicts of interest;
- The IDSA failed to follow its own procedures for appointing the 2006 panel chairman and members, enabling the chairman, who held a bias regarding the existence of chronic Lyme, to handpick a likeminded panel without scrutiny by or formal approval of the IDSA's oversight committee;
- The IDSA's 2000 and 2006 Lyme disease panels refused to accept or meaningfully consider information regarding the existence of chronic Lyme disease, once removing a panelist from the

2000 panel who dissented from the group's position on chronic Lyme disease to achieve "consensus";
- The IDSA blocked appointment of scientists and physicians with divergent views on chronic Lyme who sought to serve on the 2006 guidelines panel by informing them that the panel was fully staffed, even though it was later expanded;
- The IDSA portrayed another medical association's Lyme disease guidelines as corroborating its own when it knew that the two panels shared several authors, including the chairmen of both groups, and were working on guidelines at the same time. In allowing its panelists to serve on both groups at the same time, IDSA violated its own conflicts of interest policy.

IDSA has reached an agreement with Blumenthal's office calling for creation of a review panel to thoroughly scrutinize the 2006 Lyme disease guidelines and update or revise them if necessary. The panel -- comprised of individuals without conflicts of interest -- will comprehensively review medical and scientific evidence and hold a scientific hearing to provide a forum for additional evidence. It will then determine whether each recommendation in the 2006 Lyme disease guidelines is justified by the evidence or needs revision or updating.

Blumenthal added, "The IDSA's 2006 Lyme disease guideline panel undercut its credibility by allowing individuals with financial interests -- in drug companies, Lyme disease diagnostic tests, patents and consulting arrangements with insurance companies -- to exclude divergent medical evidence and opinion. In today's healthcare system, clinical practice guidelines have tremendous influence on the marketing of medical services and products, insurance reimbursements and treatment decisions. As a result, medical societies that publish such guidelines have a legal and moral duty to use exacting safeguards and scientific standards.

"Our investigation was always about the IDSA's guidelines process -- not the science. IDSA should be recognized for its cooperation and agreement to address the serious concerns raised by my office. Our agreement with IDSA ensures that a new, conflicts-free panel will collect and review all pertinent information, reassess each recommendation and make necessary changes.

"This Action Plan -- incorporating a conflicts screen by an independent neutral expert and a public hearing to receive additional evidence -- can serve as a model for all medical organizations and societies that publish medical guidelines. This review should strengthen the public's confidence in such critical standards."

THE GUIDELINE REVIEW PROCESS

Under its agreement with the Attorney General's Office, the IDSA will create a review panel of eight to 12 members, none of whom served on the 2006 IDSA guideline panel. The IDSA must conduct an open application process and consider all applicants.

The agreement calls for the ombudsman selected by Blumenthal's office and the IDSA to ensure that the review panel and its chairperson are free of conflicts of interest.

Blumenthal and IDSA agreed to appoint Dr. Howard A. Brody as the ombudsman. Dr. Brody is a recognized expert and author on medical ethics and conflicts of interest and the director of the Institute for Medical Humanities at the University of Texas Medical Branch. Brody authored the book, "Hooked: Ethics, the Medical Profession and the Pharmaceutical Industry."

To assure that the review panel obtains divergent information, the panel will conduct an open scientific hearing at which it will hear scientific and medical presentations from interested parties. The agreement requires the hearing to be broadcast live to the public on the Internet via the IDSA's website. The Attorney General's Office, Dr. Brody and the review panel will together finalize the list of presenters at the hearing.

Once it has collected information from its review and open hearing, the panel will assess the information and determine whether the data and evidence supports each of the recommendations in the 2006 Lyme disease guidelines.

The panel will then vote on each recommendation in the IDSA's 2006 Lyme disease guidelines on whether it is supported by the scientific evidence. At least 75 percent of panel members must vote to sustain each recommendation or it will be revised.

Once the panel has acted on each recommendation, it will have three options: make no changes, modify the guidelines in part or replace them entirely.

The panel's final report will be published on the IDSA's website.

ADDITIONAL FINDINGS OF BLUMENTHAL'S INVESTIGATION

IDSA convened panels in 2000 and 2006 to research and publish guidelines for the diagnosis and treatment of Lyme disease. Blumenthal's office found that the IDSA disregarded a 2000 panel member who argued that chronic and persistent Lyme disease exists. The 2000 panel pressured the panelist to conform to the group consensus and removed him as an author when he refused.

IDSA sought to portray a second set of Lyme disease guidelines issued by the American Academy of Neurology (AAN) as independently corroborating its findings. In fact, IDSA knew that the two panels shared key members, including the respective panel chairmen and were working on both sets of guidelines at the same time -- a violation of IDSA's conflicts of interest policy.

The resulting IDSA and AAN guidelines not only reached the same conclusions regarding the non-existence of chronic Lyme disease, their reasoning at times used strikingly similar language. Both entities, for example, dubbed symptoms persisting after treatment "Post-Lyme Syndrome" and defined it the same way.

When IDSA learned of the improper links between its panel and the AAN's panel, instead of enforcing its conflict of interest policy, it aggressively sought the AAN's endorsement to "strengthen" its guidelines' impact. The AAN panel -- particularly members who also served on the IDSA panel -- worked equally hard to win AAN's backing of IDSA's conclusions.

The two entities sought to portray each other's guidelines as separate and independent when the facts call into question that contention.

The IDSA subsequently cited AAN's supposed independent corroboration of its findings as part of its attempts to defeat federal legislation to create a Lyme disease advisory committee and state legislation supporting antibiotic therapy for chronic Lyme disease.

In a step that the British Medical Journal deemed "unusual," the IDSA included in its Lyme guidelines a statement calling them "voluntary" with "the ultimate determination of their application to be made by the physician in light of each patient's individual circumstances." In fact, United Healthcare, Health Net, Blue Cross of California, Kaiser Foundation Health Plan and other insurers have used the guidelines as justification to deny reimbursement for long-term antibiotic treatment.

Blumenthal thanked members his office who worked on the investigation: Assistant AG Thomas Ryan, former Assistant Attorney General Steven Rutstein and Paralegal Lorraine Measer under the direction of Assistant Attorney General Michael Cole, Chief of the Attorney General's Antitrust Department.

APPENDIX D

Whereas the IOM urges that persons with significant conflicts of interest be excluded from guidelines development processes, we note with alarm that several individuals identified in then Attorney General Blumenthal's investigation (2006-2008) who have patents giving them a proprietary interest in the selection of testing methods for Lyme disease; and they stood to gain financially from the outcome of vaccine development efforts; and they were involved in consulting with insurance companies drafting restrictions on reimbursements to patients for treatments which they and their physicians deemed appropriate and necessary; and they have been involved as expert witnesses, testifying against patient plaintiffs claiming harm inflicted by insurers and practitioners. Furthermore, they have been involved as expert witnesses before medical boards seeking to sanction physicians whose practices digress from IDSA guideline-recommended practices, even though the 2006 IDSA guidelines includes a *caveat* that they are not mandatory. Although some of these activities are disclosed by participants in the latest IDSA Lyme guidelines development process, such disclosure in and of itself, does not assure a fair and unbiased result. Indeed, many of the participants and their institutions have clear proprietary interests in the outcome of the guidelines they are involved in crafting.

APPENDIX E

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APPENDIX F

Presented by The New York State Coalition on Lyme and Tick-borne Diseases.

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