

Information Quality Request for Correction

Regarding frequency of EM Rash in patients with Lyme disease

March 25, 2019

Pursuant to the *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public*¹, the undersigned individuals and organizations request that inaccurate information disseminated by the Centers for Disease Control and Prevention (CDC) about the frequency of erythema migrans (EM) rash in patients with Lyme disease be corrected in all CDC publications, websites, and presentation materials.

The basis for this request is that the information lacks utility, objectivity and integrity and misleads patients, healthcare providers and research scientists. This not only can potentially result in human harm but can increase the number of long-term Lyme disease cases, worsening the current Lyme epidemic and increasing the financial impact on our country in terms of lost productivity, disability, and increased medical expenses.

Description of information

The contested information includes statements in CDC publications, web pages and presentation materials that the erythema migrans rash “occurs in 70–80% of the patients with Lyme disease.”

CDC Publications

In the CDC publication, *Tick-Borne Diseases of the United States, 5th Edition 2018*, the section on Lyme disease includes the following statement:

“The erythema migrans (EM) rash occurs in 70–80% of patients with Lyme disease.”

Corrections are needed in the print and PDF versions:

- Print: Page 28
- PDF: www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf

CDC Websites

Similar statements are found on the following web pages.

1. www.cdc.gov/ticks/tickbornediseases/lyme.html

“The erythema migrans (EM) rash occurs in 70–80% of patients with Lyme disease.”

2. www.cdc.gov/ticks/symptoms.html

“This rash occurs in approximately 70-80% of infected persons and begins at the site of a tick bite.”

3. https://www.cdc.gov/lyme/signs_symptoms/index.html

“Erythema migrans (EM) rash: Occurs in approximately 70 to 80 percent of infected persons.”

4. <https://phil.cdc.gov/Details.aspx?pid=14476>

“Rash occurs in approximately 70-80% of infected persons.”

5. <https://www.cdc.gov/nndss/conditions/lyme-disease/case-definition/2017>

“The most common clinical marker for the disease is erythema migrans (EM), the initial skin lesion that occurs in 60%-80% of patients.”

CDC Presentation Materials.

Inaccurate information about the frequency of the EM rash is also disseminated via presentation materials used by CDC's Lyme Corps program.

Problems with Quality

The assertion that an EM rash occurs in 70-80% of cases of Lyme disease is not supported by the scientific evidence reported in the majority of published research articles where this topic is explored.

This assertion stems from a 1984 study titled "Epidemiologic Features of Lyme disease in New York."² The study design introduced an inherent bias in that study participants (NYS physicians) were specifically advised by the NYS Department of Health to identify and report patients as having Lyme disease on **the sole reporting criteria** of an observed rash. The advisory included pictures of "classic" EM rashes, specifically those that had a "bull's-eye" appearance. Excluded from this study were persons with non-specific symptoms or other types of rashes who may have had Lyme disease.

This is a form of confirmation bias in research, in which study participants were selected to confirm a previous observation, rather than investigate the true incidence of EM rash in Lyme disease patients. Prior to this study, the rate of EM in Lyme disease was noted to be less than 50%.^{3,4}

This study has never been reproduced, and numerous subsequent published studies show the rate of EM in Lyme disease to be significantly less than 70-80%. In a non-human primate model, the rate of EM was 10%.⁵ This was also shown in a human case series titled "An Update on the Diagnosis and Treatment of Early Lyme disease: Focusing on the Bull's eye, You May Miss the Mark." In this study, the rate of the classic bull's-eye rash was shown to be 9%. In both of these and numerous other studies, the most common morphological feature was a small, red, raised rash around the site of a tick bite. Nearly 50% of the patients in the human case study did not develop a rash of any type.^{6,7,8}

Impact

CDC's dissemination of inaccurate information about the EM rash is compounded by the fact that healthcare providers and research scientists rely on the CDC as a source of credible information on the subject.

With the inaccurate information about the frequency of EM, patients and healthcare providers alike are given a false sense that a tick-borne disease has been avoided. Therefore, full treatment may be delayed or denied. Research shows that delayed treatment increases the rate of treatment failure.⁹

Inaccurate information about the EM rash also skews research priorities and results in critically flawed studies that use the rash as the entry criteria and/or end point. Clinical practice guidelines based on this research can lead to worse health outcomes for patients who are misdiagnosed as a result of recommendations based on the faulty evidence.

For more information about how seminal research studies based on inaccurate assumptions about the EM rash created and perpetuated Lyme disease misconceptions, see the Appendix - A Critical Reappraisal of the Science of Lyme Disease.

Recommended Actions

We request that CDC take the following actions:

1. Replace the contested statements identified in the preceding section with the following:
“The erythema migrans (EM) rash occurs in approximately 50% of the patients with Lyme disease. The classic bull’s-eye EM appears in only 9% of the cases. Absence of an EM with or without central clearing should not be used to exclude Lyme disease from the clinical diagnosis.”
2. Conduct a systematic review of scientific evidence and publish a notice in CDC’s Morbidity and Mortality Weekly Report about the frequency of EM rashes in patients with Lyme disease.

Thank you for your attention to this matter. We look forward to your timely response.

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References

- ¹ HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public <https://aspe.hhs.gov/report/hhs-guidelines-ensuring-and-maximizing-quality-objectivity-utility-and-integrity-information-disseminated-public>
- ² Epidemiologic Features of Lyme Disease in New York www.ncbi.nlm.nih.gov/pubmed/6334940
- ³ Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. www.ncbi.nlm.nih.gov/pubmed/836338
- ⁴ Erythema chronicum migrans and Lyme arthritis: epidemiologic evidence for a tick vector www.ncbi.nlm.nih.gov/pubmed/727200
- ⁵ Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to *Borrelia burgdorferi* by tick feeding <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0189071>
- ⁶ An update on the diagnosis and treatment of early Lyme disease: "focusing on the bull's eye, you may miss the mark". www.ncbi.nlm.nih.gov/pubmed/17945460
- ⁷ Diagnostic challenges of early Lyme disease: Lessons from a community case series <https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-9-79>
- ⁸ Comparison of Lyme Disease Prevalence and Disease Reporting in an Endemic Area <http://article.sapub.org/10.5923.j.microbiology.20130306.11.html>
- ⁹ The Clinical, Symptom, and Quality-of-Life Characterization of a Well-Defined Group of Patients with Post treatment Lyme Disease Syndrome www.frontiersin.org/articles/10.3389/fmed.2017.00224/full

APPENDIX A - A CRITICAL REAPPRAISAL OF THE SCIENCE OF LYME DISEASE

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The Centers for Disease Control and Prevention (CDC) holds as its mission the protection of US citizens from disease regardless of whether the disease threat is “chronic or acute, curable or preventable, human error or deliberate attack.” The CDC includes in its “Pledge to the American People” that all public health decisions will be based on the highest quality scientific data that is derived openly and objectively; to place the benefits to society above the benefits to the institution; and to treat all persons with dignity, honesty, and respect.¹

However, in the case of Lyme disease, the CDC is not fulfilling its mission or its pledge to protect the American public from a disease the organization readily acknowledges it has been underestimating for years.²

Based on epidemiological reports of notifiable diseases maintained by the CDC, Lyme disease is overall one of the top three notifiable infectious diseases in the United States. Although commonly referred to as the leading vector-borne disease in the United States, Lyme disease is second only to Chlamydia in terms of overall number of new cases annually.

The public health response to this high incidence infectious disease is not commensurate with the significant disease burden experienced by people who acquire the infection, nor to a society which must support those left sick and disabled by their Lyme disease symptoms. This disease burden stems directly from fundamental misconceptions about the nature of the bacteria, the biology of the infection that they cause, and the symptoms patients experience as a result.

How flawed seminal research studies created and perpetuated Lyme disease misconceptions

In 1977, Steere et al.³ published the first description of an “epidemic” of arthritis occurring in patients clustered in the vicinity of Lyme, Connecticut. By 1982, Wilhelm Burgdorfer, a research scientist employed by the Epidemiology Branch of NIAID, had identified a spiral-shaped bacterium in the genus *Borrelia* as the agent responsible for the disease symptoms.⁴ The bacterium was named for him shortly thereafter, and *Borrelia burgdorferi* was firmly established as “the cause” of Lyme disease.

In epidemiology research, it is common practice to seek a unique characteristic (a clinical “sign”) that can be used to definitively distinguish one condition from all others. In his search for the perfect clinical “sign,” Steere noted that a small proportion (25%) of his original group of patients had developed a very unusual rash resembling a target or “bulls-eye.” Steere incorrectly presumed that this rash, scientifically medically referred to as an “erythema migrans” or “EM” rash, was the tell-tale sign he was seeking, and this presumption has influenced scientific thought leading to research on Lyme disease since.

Basically, all subsequent studies on Lyme disease the clinical aspects of Lyme disease, included a recruitment process heavily skewed toward a population of patients who developed an EM rash as a sign of “early” infection with *Borrelia*. While we now know that the majority of Lyme patients do not ever develop this particular type of rash, this

APPENDIX A - A CRITICAL REAPPRAISAL OF THE SCIENCE OF LYME DISEASE

fundamental flaw in the original study design introduced a strong and pervasive bias into all subsequent studies on the clinical manifestations of Lyme disease. This is readily evidenced in a second paper published in 1977, in which the incidence of the EM rash in Lyme disease patients not surprisingly increased to 70%.⁵

The first epidemiological investigation of Lyme disease in New York was published in 1984 and cemented the perception that the EM rash was the hallmark sign of Lyme disease.⁶ In this study, New York State physicians were “intensively solicited” to report cases in which patients presented with an EM rash (as the primary criteria) during the months of May, June or July. Not unexpectedly, the incidence of the EM rash in patients with this disease once again increased, to a significant majority of reported cases (80%) who presented with the rash. This paper also led to the assumption that the “new” disease was one that only occurred in the summer.

Published clinical research has consistently shown that there is only a weak association between an observed EM rash and any Lyme disease symptom other than arthritis.⁷ Unfortunately, the EM rash continues to be used as a diagnostic standard, with the CDC stating that an EM will be the primary sign of Lyme disease 70-80% of the time.

Little scientific support for “Post-treatment Lyme disease syndrome”

Since their discovery and development as drugs in the 1950s, antibiotics have been considered a “magic bullet” capable of rendering all bacteria dead after brief treatment. In 1982, this was still a strongly held belief.

Therefore, once a bacterium was determined to be the cause of the epidemic of “Lyme arthritis” in the early 1980s, the next step was to determine which antibiotics should be used for treatment. The first investigation of the efficacy of antibiotic treatments for Lyme disease was published in 1983.⁸

The data presented in this seminal study indicated that nearly 50% of antibiotic treated patients still experienced debilitating symptoms post-treatment. However, the study authors concluded that for patients with “early” Lyme disease, 10 – 14 days of tetracycline was an effective treatment, with penicillin and erythromycin as acceptable alternatives. The data simply does not support the conclusions. How could the researchers reconcile data showing a high rate of treatment failure with their conclusion that 10 – 14 days of an antibiotic was an effective treatment for Lyme disease?

At the time this study was conducted, there was a strong belief that infectious diseases caused by bacteria were no longer a significant threat to human health, because antibiotics killed all bacteria and were curative. While that simplistic view has been shown in the past decade to be false and short-sighted, in 1984 data that appeared to show that antibiotics failed as an effective treatment for a bacterial infection was in direct conflict with the prevailing medical dogma.

Because the data did not support the precept, the data was rearranged in such a way to make it appear that the vast majority of Lyme disease patients recovered when a standard antibiotic regimen (10-14 days of a single antibiotic) was applied to their treatment.

The data on patient outcomes was broken down into two groups – patients who experienced “Major” symptoms after the antibiotic treatment vs. those with “Minor”

APPENDIX A - A CRITICAL REAPPRAISAL OF THE SCIENCE OF LYME DISEASE

symptoms. “Major” symptoms were those that were obviously apparent by physician observation alone, including recurrence of the EM rash and/or severe and potentially life threatening meningitis, carditis, or arthritis with noticeable swelling of the joint. Patients who experienced post-treatment “Major” symptoms were considered treatment failures. Few people in any of the treatment groups developed these “Major” conditions.

“Minor” symptoms were those that physicians would perceive as more “subjective.” Patients grouped into the “Minor” data group showed symptoms of arthritis without apparent joint swelling, tachycardia, cranial nerve palsy, peripheral neuropathy, severe fatigue, headaches, and changes in mental function. These are considered symptoms, but not signs, because they are based on a person’s description of how they feel, as opposed to being directly observable by a physician.

A critical analysis of the data presented in this first paper on antibiotic treatment of Lyme disease clearly shows that **nearly half** of the patients enrolled in this study were left with post treatment symptoms. What the authors concluded, however, was that the symptoms they personally considered to be “Minor” were unreliable clinical signs and therefore these cases did not represent treatment failure.

Other studies have yielded similar results. In one, 100% of tetracycline-treated Lyme disease patients were left with the same painful and debilitating post-treatment symptoms deemed to be “Minor” (and not treatment failures) by Steere, et.al.⁹

An unfortunate and avoidable outcome stemming from those early studies is Lyme disease patients who continue to suffer with debilitating joint pain, peripheral neuropathy, severe fatigue, tachycardia, and other symptoms after the recommended 10 – 14 days of doxycycline treatment, are now lumped into a nebulous medical state called “Post-treatment Lyme disease syndrome” or PTLDS, or sometimes, “Medically Unexplained Symptoms.” This moniker incorrectly implies that the original infection was successfully treated and that the symptoms are due to some other disease state, just not Lyme.

Why do nearly half of people infected with *Borrelia* experience debilitating symptoms of Lyme disease after the standard treatment of 10-14 days of an antibiotic? Current competing hypotheses to explain so-called PTLDS include (1) continuing infection by the bacteria that survive the antibiotic treatment causing chronic inflammation, (2) the presence of remnants (including DNA) of dead bacteria in tissues causing chronic inflammation, or (3) an autoimmune type of reaction, or (4) the overactive imaginations of people with nothing better to do than complain to their doctors about the pain of their daily lives.

The preponderance of the scientific evidence strongly points to persisting infection by antibiotic tolerant forms of several different *Borrelia* genospecies, and likely coinfection with other tick-borne microorganisms, as the underlying cause of the chronic disease symptoms seen in both untreated and treated Lyme disease patients. Past and present research on the biology of *Borrelia* provides considerable insight into how these bacteria are able to cause chronic disease in humans

The remarkable biology of *Borrelia*¹⁰

Borrelia are a type of bacterium called a spirochete, based on their appearance as a slender rod with a twisted shape when observed under the microscope. Spirochetes are

Information Quality Request for Correction – Page 6

APPENDIX A - A CRITICAL REAPPRAISAL OF THE SCIENCE OF LYME DISEASE

known to drill through tissue to reach sites in the body the immune system can't reach, such as the central and peripheral nervous system (brain and nerves), and collagen dense non-vascular tissues such as tendons and cartilage (joints).

As a biological group, *Borrelia* are obligate parasites that rely on an animal host to survive. Their biology is vastly different from other bacteria. The features that make *Borrelia* unique are not in any way incorporated into the prevailing medical opinion about the clinical manifestations of Lyme disease in humans.

Borrelia have an exceptionally complex genome with numerous genes that appear to be unique among bacteria. Because they did not evolve to infect humans, *Borrelia* lack genes for the classic bacterial virulence factors, like toxins and lipopolysaccharide. The genome appears to be a state of rapid evolution and there is substantial genetic variation among the various genospecies. The different genospecies of *Borrelia* elicit distinct antibody profiles, which makes them difficult to detect by classic Lyme disease blood tests relying on a strong immune response against one single genospecies, *Borrelia burgdorferi*. The different *Borrelia* genospecies are also known to localize to different host niches, and therefore create differential clinical manifestations in patients.

Borrelia are unique in their ability to exist in different shapes and forms. Although best known for the slender, twisted spirochete shape, *Borrelia* also develop dormant forms called “persisters” which have little or no metabolic activity such as protein synthesis or DNA replication. The majority of antibiotics work against bacteria by disrupting their cellular metabolism, and therefore persister forms, which lack metabolism, are unaffected. Recently it has also been shown that each of the two forms elicits different profiles of antibodies by the host immune system.¹¹ Combined, these findings explain why a few weeks of antibiotics does not always result in resolution of disease symptoms, and also provides a partial explanation of why blood tests that require a strong and singular type of immune response are inadequate for diagnosis of this disease.

In nature, *Borrelia* is at home in small mammal species such as mice, which are referred to as a “reservoir” host, where the bacteria live peacefully as a “commensal” and constitute part of the mouse microbiome. Commensal microorganisms generally do not trigger “sterilizing” immunity in their natural host animal, which is commonly noted when the natural host has a relatively short lifespan. Therefore in mice and other reservoir hosts, *Borrelia* infection is persistent, and although mice develop antibodies against the bacteria, the infection generally does not lead to disease.

Humans and other animals get infected with *Borrelia* by way of a spillover event where the bacteria are transferred when a blood-sucking tick (called the “vector” in the transmission cycle) acquires the bacteria when it feeds on an infected reservoir. This implies that the bacteria are found in circulating blood, probably in small numbers.

When injected into a new host animal, such as a dog, horse, monkey or a human, infection is not a peaceful coexistence as it was in the reservoir, because humans are not the natural host. Disease symptoms occur largely as a result of activation of the host innate immune response which triggers inflammation. Whereas infections by other bacteria trigger a cascade of immune events leading to production of a secondary, longer lived and sterilizing type of (adaptive) immune response, in humans and a few other animal species (including dogs, horses and non-human primates), *Borrelia* is able to

APPENDIX A - A CRITICAL REAPPRAISAL OF THE SCIENCE OF LYME DISEASE

totally subvert this process which allows it to establish a persistent infection. The presence of the persisting microbes drives chronic inflammation.

Notably, a significant recent research finding shows that antibiotic tolerance due to *Borrelia* persists is actually **induced** by exposure to the antibiotics routinely used as front-line treatment approaches.¹²

Recently published research has revealed that upon exiting the bloodstream, they set up permanent residence communities called “biofilms.” *Borrelia* is known to localize to the collagen containing tissues – skin, the joints, the linings of the heart, and the membranes of the central and peripheral nervous system, from where they sometimes spill into the highly protected interior and cause meningitis. Biofilms of *Borrelia* have been directly observed in studies conducted on culture-grown bacteria, and now also have been shown to form biofilms in human tissues.¹³

Persistent infections by *Borrelia*, relying on biofilm growth and persistent round body forms, are the rule and not the exception for these bacteria. This has been repeatedly, and conclusively, shown in numerous studies conducted on animal models (mice, hamsters, dogs, non-human primates) of Lyme disease. This calls into question the false and circular argument of there being “No Evidence” for persistent infection as the cause of persisting symptoms in patients who remain sick after 10-14 days of doxycycline (the current standard treatment for Lyme disease).

There is, in fact, considerable evidence that persisting infection is the cause or contributes to the pre- and post-treatment chronic pain and neurological issues experienced by 50% of Lyme disease patients. A lack of research on the cause of these symptoms **in humans** is not the same as “no evidence.” However, the type of scientific research needed to understand the sequence of events that occurs following infection with *Borrelia*, cannot be done ethically using humans as subjects. Nor will the type of poorly designed research that currently predominates, which rejects the inclusion of human subjects with any symptoms other than an EM rash or positive blood test, yield any useful information on the cause and treatment of this complex disease.

Ironically, for many other diseases the results obtained from studying animals are factored into the medical understanding and approaches to diagnosis and treatment of the disease. Not, however, for Lyme disease.

Although the CDC insists the proportion of Lyme disease patients who have continuing disease after short term antibiotic treatment is in the range of 10-20%, most evaluations, including the early studies, indicate this number to be significantly higher (30-50%).

Biological Implications for Diagnosis and Treatment of Lyme disease

As mentioned previously, human infections by *Borrelia* trigger inflammation and other early immune responses, but largely fail to generate long-term protective immunity. There are several biological reasons to explain why the current lab tests for Lyme disease, which measure the level of antibodies produced as a result of infection (and not the infection itself), including those listed below:¹⁴

- The bacteria deceive alternative complement pathways by masking surface antigens and subvert the host’s plasminogen activating system.

APPENDIX A - A CRITICAL REAPPRAISAL OF THE SCIENCE OF LYME DISEASE

- They constantly vary surface antigens which leads to low levels of detectable circulating antibodies.
- When active in the spirochete form, the bacteria move using uniquely agile motility skills, and locate to immunologically protected tissue in the host.
- *Borrelia* cells assume different shapes, which are physically, metabolically, and immunologically distinct from the spirochete form. Persister forms tolerate antibiotic challenge and reactivate after antibiotic exposure ends.
- *Borrelia* engage in quorum sensing and grow in biofilms.
- They continuously share DNA with other bacteria and quite probably with the animal cells they invade, through horizontal gene transfer (HGT).

Using the strategies above, and also by invading cells and existing intracellularly, *Borrelia* circumvent the process by which the immune system produces antibodies, the guided missile molecules of the immune system. The current diagnostic “gold standard” for Lyme disease diagnostics depends entirely on an infected human producing an abundance of antibodies, specific for only a single genospecies (*Borrelia burgdorferi*).

Numerous studies point out the inadequacy of the standard serological tests for diagnosis of Lyme disease.¹⁵ Virginia and now Maryland have passed laws stipulating that physicians must inform their patients that a negative result on a blood test does not necessarily mean you don't have Lyme disease.

Why the medical construct of Lyme disease must be revised to match the science

In summary, the current medical construct of Lyme disease, which has its roots in 1977 but had largely stopped evolving with new science by 1984, describes a disease that is entirely inconsistent with the disease as it is experienced by patients. Clinically, the current medical construct is of an infectious disease caused by one single genospecies of a specific bacterium (*Borrelia burgdorferi*), and that the initial infection leaves behind a tell-tale rash as a clear objective sign for the majority of Lyme disease cases. This infection is considered to be easily treatable with routine doses of antibiotics, and patients recover fully. Unfortunately, a sizeable body of scientific information has been excluded from the Lyme disease definition.

A complete and unbiased review of the scientific literature shows clearly that the current Lyme disease construct is only one form of the disease, which is actually experienced by only a minority of patients. The disease rarely begins with an EM rash, and nearly 50% of the time evolves into a disabling chronic disease with a myriad of symptoms. The current “gold standard” blood test for Lyme disease detects high levels of antibodies produced by an infected person against *Borrelia burgdorferi*. Research shows, however, that *B. burgdorferi* is only one of many disease-causing genospecies of *Borrelia*, and that the bacteria actually shut down the branch of the immune system responsible for producing antibodies. Existing and emerging research shows that in nature, most genospecies of *Borrelia* cause persistent infections in animals, including humans. This same body of science also strongly implicates coinfections with other tick-borne microbes as the cause of at least some of the complications surrounding Lyme disease diagnosis and treatment.

APPENDIX A - A CRITICAL REAPPRAISAL OF THE SCIENCE OF LYME DISEASE

All of the meager scientific data accumulated from studies done with human subjects indicates that short-term antibiotic treatment may be an effective treatment for EM rash, but it is not an effective treatment for the other symptoms, those subjective, “Minor” symptoms experienced by nearly 50% of patients. More research on treatment approaches for all forms of the disease are desperately needed.

At present, research that should have begun 30 years ago under leadership from the NIH and CDC (but has not occurred), is finally underway thanks to funding from private philanthropic individuals and groups. There is hope that this research will lead the way to a broader recognition on the part of these federal agencies of the burden that Lyme disease places on both individuals and society, and a long overdue commitment of federal resources to address the public health disaster that Lyme disease has been allowed to become.

References:

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- ² CDC.gov <http://www.cdc.gov/media/releases/2013/p0819-lyme-disease.html>
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