Finally, a Shot to Prevent Lyme Disease Could Be on Its Way

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Lyme-carrying ticks are a bigger threat than ever. A promising new antibody treatment looks to stop infection—even after a tick bite.

Bart Yasso was never more himself than when he was on a long run. As the chief running officer of *Runner's World* magazine, he generally logged about 80 miles per week. He regularly trained for marathons and had finished two Ironmans, taking comfort in the distances he traveled. That all changed one cool April day in 1990.

After running a 50-mile ultramarathon around Lake Waramaug in Connecticut, Yasso lay down in a grassy field to recuperate before his drive back to Pennsylvania. A week later, he started feeling sick, unusually fatigued, and achy. He had a fever. On his neck, he found a red rash in the shape of a bull's-eye. Yasso had never seen anything like it, and he had no idea what it was.

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“I went through a series of doctors, and no one could figure out why I was just not feeling well,” Yasso recalls. “I’d try to run every once in a while, but it was awful.”

Awareness around Lyme disease was limited back then. It was a regional infection, confined mostly to the Northeast and near the Great Lakes. While his fever and rash eventually abated, Yasso lived with aching joints for weeks, going to doctor after doctor, trying to figure out what was wrong. It wasn’t until three months later that he was finally diagnosed with Lyme.

Unfortunately for Yasso, the experience was merely the prologue for what was to come, as he contracted Lyme disease another three times over the next 30 years. As a result, he experiences swelling and pain in his joints. “To have swollen joints before you even head out the door on your run is not good,” he says. “I want to run. I try to run. Most days I just can’t.”

Lyme is treatable, and most people who are infected recover after a month of antibiotics if the disease is caught early. But the number of cases has risen sharply over the past decade, and scientists are now directing their efforts toward novel therapies. The goal is to prevent infection even after a tick bite occurs—and possibly crush Lyme disease as we know it.

In 1975, two mothers living near Lyme, Connecticut, reported an outbreak of juvenile arthritis among 39 children. Field interviews by rheumatologist Allen Steere, from the Yale School of Medicine, and David Snydman, from the state health department, revealed striking similarities between many of the patients. They all lived in wooded areas of town. Many said their symptoms occurred between June and September. Most notably, a quarter of them also reported a red skin lesion, shaped like a bull’s-eye, that appeared about four weeks before their arthritis began.

Steere knew from his research that at a 1909 meeting of the Swedish Dermatological Society, the attendees had discussed the same sort of skin lesion. They hypothesized that a tick bite was the cause, which led Steere and Snydman’s investigative team toward the same conclusion. They confirmed their hunch in 1978, after discovering that incidents of this strange arthritis were 30 times greater on the east side of the Connecticut River, where the town of Lyme is located and a much larger population of ticks resided. Then, in 1981, Willy Burgdorfer, a researcher with the National Institutes of Health (NIH), discovered the cause: a spiral-shaped bacterium, known as a spirochete, that passed from tick to human after a bite. He published his findings in 1982, and the Lyme-causing microbe was christened *Borrelia burgdorferi*.

While the Northeast and the upper Midwest are still the hot spots, the infection has gradually expanded its reach. There are now confirmed cases in all 50 states and Washington, D.C., and almost 100 million people live in areas where instances of Lyme are at their highest. Over the past two decades, incidents of Lyme disease have exploded: the Centers for Disease Control and Prevention estimates that 476,000 Americans are diagnosed and treated for Lyme each year, making it the most common vector-borne disease in the U.S. Recent research shows that people living in the Northeast take one billion fewer excursions than they otherwise would in order to avoid Lyme-carrying ticks.

“Now they’re found in places where we didn’t really see them 20 years ago,” says Amy Schwartz, an epidemiologist with the CDC’s division of vector-borne diseases. “It’s hard to know exactly what has happened.”

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The black-legged tick, *Ixodes scapularis*, transmits Lyme disease in the Northeast and Midwest. (It's also called the deer tick, a nod to its preferred animal host, the white-tailed deer.) In the western U.S., a related black-legged tick, *Ixodes pacificus*, is the Lyme disease vector. Larval ticks feed on mice, common animal carriers of *Borrelia*, in the fall. Sitting deep in the tick's gut, the bacterium effectively goes comatose. From May into July, the larvae turn into nymphs, and that's when they strike, straight through summer. Warming temperatures and a booming population of deer, upon which Lyme-carrying ticks usually hitchhike their way to other places, are likely culprits for the disease's expanding geographic range.

When a black-legged tick latches on to a host, it spits anticoagulant into the cut and starts drinking. Warm, hemoglobin-rich blood reaches its gut, prompting *Borrelia* to wake up, multiply 20 times over, and migrate to the tick's salivary glands. The whole process takes about 36 hours. "Even if you have an infected tick attached to you, if you remove it within a day, it doesn't matter," says Sam Telford, a Tufts University professor of infectious diseases. It's only after 36 hours that the problems start: now that the bacteria have arisen, multiplied, and traveled to the salivary glands, they're ready to be spit into your bloodstream.

Even today, diagnosing Lyme disease can be a challenge in some cases, largely because early symptoms of Lyme mirror those of the flu. A bull's-eye rash around the site of a tick bite is a dead giveaway, but according to the CDC, only about three-quarters of people who contract Lyme will develop that rash. The rest are only hit with a fever, fatigue, headaches, and swollen joints.

A blood test usually confirms whether a person has Lyme disease, but there's a slight wrinkle: the test doesn't look for the physical presence of the Lyme microbe, which could confirm an ongoing or active infection or an infection that was wiped out. Instead, it searches only for Lyme antibodies—and not that reliably. An analysis published in 2016 in the journal *PLOS One* found that such tests are accurate just 60 percent of the time. Get tested too quickly, before antibodies develop, and you don't know if you have Lyme disease. And antibodies may never appear in people with compromised or weak immune systems; those patients may have Lyme, but doctors can't know for sure.

According to current guidelines from the Infectious Diseases Society of America, several weeks of oral antibiotics immobilize Lyme microbes. Still, the NIH says that in as many as 20 percent of cases, antibiotics fail to stop the bacteria. And each extra day that Lyme-causing *Borrelia* persists gives it time to spread further, invading organs such as the heart and the brain, as well as various joints. Original symptoms, like joint arthritis, can become more severe. Meanwhile, in rarer cases, infection in the brain can lead to cognitive difficulty and sleep disorders, while Lyme that affects the heart can lead to blocks of the electrical signals that make it pump blood effectively. If Lyme spreads that far, oral antibiotics are usually paired with amoxicillin administered through an IV.

When it comes to tick-borne diseases, "*Borrelia* is the toughest nut to crack," says Monica Embers, a Lyme expert and director of vector-borne disease research at Tulane National Primate Research Center near New Orleans.

Often the best defense is keeping ticks from biting in the first place, and that usually boils down to being smart when outdoors. Telford, who spends his summers in the woods collecting ticks for study, recommends long sleeves and pants or clothes treated with permethrin, an insecticide. What's missing from the tool kit, though, is a way to stop the disease outright, even in the event of a tick bite.

No human vaccine is available for Lyme disease, despite all the trouble it causes. In Yasso's case, oral antibiotics were never enough. He's been prescribed a variety of antimicrobial treatments, including blood radiation, a relatively uncommon treatment for Lyme in which doctors siphon some blood, blast it with electromagnetic waves, and then drip it back into the bloodstream. "Every time I do these treatments, I feel better. But it's only temporary," he says. "Sometimes it'll last three months. Sometimes it'll last a month."

Yasso's ongoing struggles place him in a rare group: for about one in five people who contract Lyme, the disease morphs into a ceaseless condition with persistent symptoms. It's what the CDC recognizes as "post-treatment Lyme disease syndrome." As of 2020, about two million people in the U.S. were dealing with this syndrome, characterized by fatigue, headaches, problems with concentration and memory, and painful arthritis.

There's another term for these cases of long Lyme disease, a subject of acrimony and division within the medical community: chronic Lyme. The Infectious Diseases Society of America, in fact, doesn't recognize chronic Lyme as an official diagnosis. Writing in *The Atlantic* in 2019, Meghan O'Rourke reported that, in the IDSA's view, chronic Lyme is "a pseudoscientific diagnosis—an ideology rather than a biological reality."

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Two schools of thought reign, according to Tulane's Embers: On the one hand, there are doctors who say that Lyme symptoms will persist in some patients even after antibiotic treatment, and that will lead to chronic Lyme. (In other words, there's an active infection. A study published in 2018 found "persistent *Borrelia* infection despite antibiotic therapy in patients with ongoing Lyme disease symptoms.") On the other hand, some medical professionals argue that antibiotics always treat Lyme symptoms, and therefore any lingering issues a patient has afterward must be due to something else.

Still, science can agree on one thing: not contracting Lyme disease in the first place is best. To that end, some scientists have mobilized to tackle the Lyme problem by flipping the script. Forget treating *Borrelia* in the body. What if you could immobilize it while it was still inside the tick?

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Enter Mark Klempner. A physician and infectious-disease scientist at the University of Massachusetts, he's embarked on an experiment that could upend the field of Lyme treatment. Klempner is the lead creator of a first-of-its-kind antibody shot for preventing Lyme infection. The idea is to administer the injection annually, so that people are protected from late spring through early fall.

Bespectacled and friendly, Klempner, now in his early seventies, has a reassuring air about him. He comes across as insatiably curious, the product of a life spent trying to unravel medical conundrums.

A trip to Nigeria in 1972 decided the trajectory of his career in health care. While working in a field hospital, he treated patients with malaria, measles, and tuberculosis. When he graduated from Cornell University Medical College in 1973, he knew he wanted to study infectious diseases. In his third year of medical school he applied for a fellowship at the NIH, at the encouragement of the college's chief resident, Anthony Fauci. (You may have heard of him.) Klempner arrived for a three-year stint in 1975—the same year that juvenile arthritis was first reported in Lyme, Connecticut.

"I spent quite a bit of time looking at the host response to infectious agents, so I knew a lot about how the body fought off infections," he says. "Then came Lyme disease, and nobody knew how your body fought it off."

Klempner spent years researching Lyme disease. He even took a summer sabbatical in 1990 to work with Burgdorfer at Rocky Mountain Laboratories in Montana, where the pioneering studies on *Borrelia* took place. Klempner went on to head up MassBiologics, the country's only nonprofit vaccine manufacturer licensed by the Food and Drug Administration. (In July, he transitioned from that role into one that focuses on the clinical development of medicines in the nonprofit's pipeline.) Having learned how the body fights Lyme, Klempner turned his attention, in 2014, to coming up with a preventative medication.

The Lyme microbe is a tough adversary, with a wide reach. There are 18 known species of *Borrelia* across North America, Europe, and Asia that cause Lyme disease. But it does have a weakness, which Klempner aimed to exploit: the bacterium's exterior is covered with outer surface proteins that govern its behavior. Outer surface protein A (OspA) coats the microbe while it's inside the tick, allowing it to stick to the gut walls. Once the tick bites someone and starts drinking blood, microbes slowly shed OspA in favor of outer surface protein C (OspC), which helps the bacteria move from the gut to the salivary glands and, from there, to the bloodstream, where this new protein jacket further helps it evade the human immune system.

Klempner's idea was simple: find an antibody that neutralizes OspA, spin it up into an injectable solution, and inoculate someone. The discovery and development involved a host of scientists and clinicians from MassBiologics and elsewhere. Called Lyme PREP (for "pre-exposure prophylaxis"), the treatment delivers many identical Lyme-microbe-fighting antibodies directly into the bloodstream. (It's the same sort of monoclonal antibody approach that's used to treat some COVID-19 patients.) When a tick latches on and starts drinking, it sucks the antibodies right into its gut, stopping *Borrelia* bacteria. "You're trying to block

transmission before you even get the bacteria in you," Klempner says.

At its highest dosage, Lyme PREP was 100 percent effective in mice and nonhuman primates. (Embers actually helped Klempner and his team conduct studies on nonhuman primates in Massachusetts.) Still, that's no guarantee of crossover success in people. Mice are carriers of Lyme microbes, and yet they don't get sick from the infection. And while primates are our close mammalian cousins, they're just a substitute for the real test. Earlier this year, Lyme PREP entered its first clinical trials in humans.

A decade ago, 300,000 Americans would contract Lyme in a year. Now, with numbers rising, and because of how tricky the disease is to eradicate in some people, a pre-Lyme treatment that works well could be huge. "It's pretty well accepted that the longer the infection goes, the more difficult it is to treat," Embers says. "If we can prevent infection, that would really be a game changer."

Dr. Mark Klempner (Courtesy MassBiologics)

Bart Yasso (Courtesy Bart Yasso)

While Klempner's antibody injection is novel, the strategy he's employing isn't entirely new—and it fits into a complicated history of scientific efforts to try and stamp out Lyme disease.

In the late 1990s, a scientific race was on to create the first Lyme disease vaccine. In 1998, SmithKline Beecham (now GlaxoSmithKline) received FDA approval for a vaccine called Lymerix. It was designed as a transmission-blocking vaccine: Lymerix stimulated the immune system to generate OspA antibodies, which, when ingested by the tick during its blood meal, would immobilize the *Borrelia* sitting in its belly.

While no vaccine is perfect, the limitations of Lymerix quickly became apparent. For one, it was only approved for use in people ages 15 to 70. Full vaccination required three shots over 12 months, and each dose was $50, a cost not always covered by insurance. It was unclear how long immunity lasted post-vaccination. Plus, people react differently to vaccines. There's always the possibility that someone produces a weak antibody response after vaccination—leaving their level of protection unclear.

Klempner participated in that earlier Lyme vaccine race. He was one of the investigators of the competing vaccine, ImuLyme. Both Lymerix and ImuLyme were found to be anywhere from 76 to 92 percent effective in preventing the disease after three injections. (Compare that to the measles vaccine, which is 93 percent effective after one dose, and 97 percent effective after two.) Yet Lymerix beat it to the market, which might be why ImuLyme's manufacturer never sought federal approval.

Despite its shortcomings, Lymerix was initially popular. By July 2000, more than one million doses had been distributed. But safety concerns eventually sank the vaccine. While the FDA panel that approved Lymerix did so unanimously, several members wondered whether the vaccine might cause an autoimmune reaction leading to arthritis. A section of OspA resembles a human protein that modulates the immune response, and the concern of some on the FDA panel was that, after vaccination, the immune system would overcorrect and fight off not only the OspA protein that covered the bacteria, but also that human protein. Nothing like this occurred in Lymerix's clinical trials.

Shortly after Lymerix hit the market, those worries emerged nonetheless. Some recipients reported joint pain and arthritis, symptoms they blamed on the vaccine itself. The FDA found only 59 such adverse events out of 1.4 million doses administered, and did not find direct scientific evidence that the Lyme vaccine had caused them. Still, the questions over possible unintended effects were enough to dampen enthusiasm, especially after 121 Lymerix recipients filed a class-action lawsuit against the vaccine's manufacturer. SmithKline Beecham, projecting sales of only 10,000 doses in 2002, decided to withdraw Lymerix from the market in February of that year. (The lawsuit was settled one year later, with more than $1 million paid out by the pharmaceutical company to cover the prosecuting lawyers' fees, but no financial compensation was awarded to the plaintiffs.)

"Because of that experience, it took a long time before any company would even approach Lyme disease vaccines with a ten-foot pole," says Tufts University's Telford, who helped run the Lymerix clinical trials.

To this day, Lyme advocacy groups are leery of any proposals to use OspA in a vaccine. Klempner's approach is objectively different: Lymerix was a vaccine that showed the body the OspA protein in order to get the immune system to make antibodies to fight it—the interaction where the concern lay over autoimmune reactions. Lyme PREP, instead, is an injection of just those antibodies.

"That's the beauty of Mark Klempner's approach," Telford says. "People objected to the OspA vaccine, because they thought the protein itself was harmful. Here, you're not seeing the protein, you're just seeing what you wanted the protein to generate."

At the same time that some doctors were talking up Lymerix, other doctors remained skeptical about the necessity of a vaccine. Why vaccinate against something that can be cured with antibiotics? The split marked the early stage of the debate over chronic Lyme. If antibiotics treat the infection, then the people who exhibit ongoing musculoskeletal pain, cognitive impairment, and fatigue must be suffering from something other than Lyme disease. (Again, as O'Rourke reported, a program officer working for the NIH in 2007 sent an email that labeled people who insisted they had chronic Lyme disease as "Lyme loonies.")

Yet according to Embers, some people who contract Lyme still suffer from symptoms after taking antibiotics—and sometimes without a detectable infection. That the current blood tests for Lyme are just antibody tests compounds the problem.

“We don’t really have any way to tell whether a patient is persistently infected or not, so therein lies the conundrum,” says Embers. “And I’m not saying that everybody that’s treated with antibiotics has a persistent infection after treatment. In most cases, the antibiotics are curative, but in a proportion of them, they are not.”

Meanwhile, studies Embers has conducted on nonhuman primates at Tulane University show that spiral-shaped Lyme bacteria remain in the animals even after a course of antibiotics. In May, her research team published their strongest evidence to date of persistent Lyme symptoms. In a unique finding, they discovered Lyme bacteria in the tissues of a deceased 69-year-old woman who contracted the disease, was treated multiple times with antibiotics, and still couldn’t clear the infection from her body.

“It’s frightening,” Embers says. “After the extensive course of antibiotics, most clinicians would rule out persistent *Borrelia* infection as a potential cause for her decline. But the spirochetes were there, in her spinal cord and brain.”

Controversy over chronic Lyme, and what to do about it, is well-known to Klempner. In 2001, he wrote the first study on whether to use antibiotics long-term in order to cure lingering symptoms of Lyme. His conclusions went against the idea of continually prescribing rounds of antibiotics, since there are risks to ongoing usage (for instance, damage to good gut bacteria). Yet Klempner says that because the medical community has failed to embrace the notion of an active infection as the cause of chronic Lyme, developing treatments to prevent Lyme disease has been tougher.

“It’s just an unfortunate hurdle that is in our way. Because I think we all want the same thing—we all want fewer people to get Lyme disease,” Klempner says. “I expect Lyme PREP will work. I expect it will be safe. But I think it’s going to fight the acceptance battle.”

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It’s the same battle that several other therapeutics for Lyme disease may end up fighting as well. An oral medication being developed by a California biopharmaceutical company is in phase-one trials in people. A French biotech company, Valneva, is currently running phase-two clinical trials in the U.S. and Europe for a Lyme disease vaccine. Valneva signed a deal with Pfizer last year to commercialize what it’s calling VLA15.

In February, Klempner’s phase-one trial kicked off with 60 participants. The goal of the trial is to determine the right dosage so that a person is protected for six to eight months. Lyme PREP will have to be administered annually, but it’s a small price to pay in the minds of infectious-disease experts. “If my

administered annually, but it's a small price to pay in the minds of infectious disease experts. "If my forehead looks flat, it's because I have been banging my head on the wall for 35 years," says Telford. "We need as many tools as possible to prevent Lyme disease."

In just a few years, Lyme PREP could be available for commercial use. Klempner is eyeballing 2024, and maybe even sooner, depending on how the drug performs in clinical trials.

When that day comes, Bart Yasso plans to be first in line. "I would tell every person I know to take it, and every runner for sure," he says. He retired from his post at *Runner's World* in 2018, at age 62. That was shortly after he contracted Lyme disease a fourth time. It continues to make running difficult; these days, he usually averages just 15 miles a week. There's always some pain. But every so often, Yasso laces up his sneakers and starts out. One foot hits the pavement, then the other, and as he falls into his familiar cadence, a different sensation washes over him. He runs, and for a brief moment, just like that spring morning in 1990, he feels fine.

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