Lyme vaccines: Are scientists closer to hitting the bullseye?

By Danielle Harper

It's been 20 years since the only FDA-approved Lyme vaccine was pulled from the market, but a new shot could be on the horizon.

In 1975, children in the rural town of Lyme, Connecticut, began experiencing recurrent bouts of arthritis after developing an unusual bullseye-shaped rash. The condition was quickly traced to a spirochete bacterium, *Borrelia* (*B.*) *burgdorferi*, transmitted through the bite of infected blacklegged ticks (of the Ixodes genus).[1] Today, Lyme disease is one of the most common insect-borne illnesses worldwide, with almost half a million cases per year in the U.S. alone.[2]

Early-stage Lyme-disease results in mild-symptoms including muscle ache, joint stiffness, headache, and fever.[3] Some patients may not experience any symptoms, but the most obvious sign of early infection is the distinctive bullseye rash, known as erythema migrans. Most patients respond well to a course of antibiotics, such as doxycycline, but if left untreated Lyme disease can result in serious cardiac and neurological complications, in addition to chronic rheumatoid arthritis. [3]

As climate change continues to make summers longer and winters milder, tick season has worsened across many parts of the world. Regions previously untouched by these pests have become epicentres for Lyme Disease. In Canada, the number of confirmed cases jumped from 144 in 2009 to 2634 in 2019,[4] although experts agree that these numbers are likely even higher due to underreporting.[5]

Current recommendations for the prevention of Lyme Disease focus on avoiding *B. burgdorferi* transmission using tick repellents (such as DEET), and the prompt removal of ticks that have embedded themselves in the skin.[6] While these methods are effective at reducing the likelihood of tick bites and subsequent bacterial transmission, they offer no protection once an individual has become infected. The quest for an effective vaccine against *B. burgdorferi* infection has been steeped with challenges, and while there are several commercially available shots for dogs (LymeVax®, Nobivac® Lyme, RECOMBITEK® and VANGUARD®), there are presently no clinically approved Lyme vaccines for humans.

Recently, several groups have reported promising progress on the vaccine front, offering a new ray of hope following the dismal failure of SmithKlein Beecham's LYMErix vaccine in the early 2000s.[7] Approved by the U.S. Food and Drug Administration (FDA) in 1998, LIMErix was designed to stimulate an immune response against a protein found on the surface of B. burgdorferi, called outer-surface protein A (OspA). FDA approval requires three phases of testing. Phase I clinical trials evaluate vaccine safety in a small group of healthy volunteers. Phase II trials assess the effectiveness of the vaccine, as well as potential side effects, in a larger group of participants (typically several hundred), and phase III trials include thousands of patients to evaluate the safety and efficacy of the vaccine on a much larger scale. Post-market surveillance continues to monitor long-term effects of the vaccine, and FDA approval may be revoked if safety concerns arise.

LIMErix showed promise in phase III trials but reports of adverse effects began to surface shortly after its approval.[7] Between December 1998 and July 2000, more than 1.4 million doses of LIMErix were administered to patients across the United States.[8] A total of 905 adverse events were reported during this time ranging from muscle and joint aches/pains (~600 reports) to arthritis (~60 reports) to allergic reactions (22 reports).[8] Researchers determined that these reports were neither unexpected nor unusual based on previous observations from clinical trials.[8] However, extensive media coverage fuelled public concerns and the manufacturer of LIMErix decided to pull the vaccine from the market following a decline in sales, despite the FDA not revoking its approval.[7] Two decades have passed with no new Lyme vaccine, but promising preclinical and clinical studies suggest that the next Lyme vaccine could be right around the corner.

The leading vaccine contender is being developed by the French biotech company, Valneva, in partnership with Pfizer. Like LIMErix, Valneva's vaccine, VLA15, uses OspA to confer immunity against Lyme infection.[9] VLA15 provides broad protection against several Borrelia species by incorporating subunits from six variations of the OspA surface protein into the vaccine.[9] In addition to *B. burgdorferi*, there are several other bacteria known to cause Lyme disease including *B. afzelii*, *B. garinii* and *B. bavariensis*. By incorporating six variations of OspA, VLA15 aims to protect against most Lyme-causing bacteria found around the world.[9] In 2017, the FDA granted "Fast Track Designation" to VLA15 to expedite its development.[10] The vaccine has shown promising results in Phase II clinical trials, with no vaccine-related serious adverse events reported. The vaccine is scheduled to move into Phase III trials later this year, using a three-dose schedule, administered 4 weeks apart.[11]

While it has not yet reached human trials, another vaccine candidate is gaining attention based on positive laboratory findings. Researchers at Yale University recently described a novel mRNA vaccine, known as 19ISP, based on proteins found in the saliva of the black-legged tick, Ixodes scapularis.[12] mRNA vaccines have gained much attention amidst the coronavirus pandemic, but scientists have been studying their potential for decades. mRNA vaccines contain messenger RNA (mRNA) that provides a patient's cells with instructions make a particular protein associated with the pathogen of interest. The 19ISP vaccine contains instructions for 19 proteins known to be produced inside the salivary glands of *I. scapularis* ticks. Previous studies conducted in guinea pigs found that antigens present on these 19 proteins were able to promote a host immune response against tick bites.[12] Antigens are distinct molecular structures that the body recognizes as foreign and mounts an immune response against. Guinea pigs immunized with 19ISP acquired resistance to tick feeding and demonstrated by early detachment of ticks from the skin, preventing *B. burgdorferi* transmission.[12] More work is needed before 19ISP can transition to human trials, but these exciting preliminary results suggest that an mRNA vaccine may offer a novel alternative for Lyme disease prevention.

Traditionally, Lyme prevention has focused on avoiding tick bites altogether, but the growing prevalence of ticks, attributed to climate change, underscores the need for an effective vaccine. VLA15 and 19ISP represent two exciting developments in the field of Lyme prevention and have brought scientists one step closer to hitting the bullseye.

Erythema migrans, also known as the "bullseye".
Photo courtesy of Brian Laight

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