Lyme disease vaccines face familiar challenges, both societal and scientific

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Just over 20 years ago, a Lyme disease vaccine called LYMErix was approved for sale in the United States. Researchers designed the vaccine to prevent the transmission of the tick-borne pathogen *Borellia burgdorferi*, which spurs a bacterial infection that can cause fever, headaches, and joint pain if left untreated.

LYMErix was on the market for just four years. Concerns over adverse reactions and a lukewarm reception from public health agencies led the vaccine's manufacturer, SmithKline Beecham, to shelve the product in 2002. Since then, the need for a vaccine has grown. An estimated 300,000 people are diagnosed with Lyme disease in the United States annually, and reported cases of the disease have tripled since the 1990s. In some counties in the northeast United States, disease incidence has increased more than 300% over a 20-year period. "The people who live along the northeast corridor among the Mississippi River valley have suffered greatly because there is no Lyme vaccine," says Gregory Poland, a vaccine researcher at the Mayo Clinic in Rochester, MN.

Now, a new round of Lyme disease vaccines is in development. European biotech company Valneva is in phase 2 clinical trials for a vaccine against six strains of *Borrelia*, which causes the disease in Europe and the United States. And researchers are working to develop a vaccine against Lyme disease based on a vaccine for dogs that was released in 2016. The pressure is on this time around to make the "perfect vaccine," says immunologist Richard Marconi at the Virginia Commonwealth University in Richmond, one of the researchers working on the dog vaccine–inspired approach.

The black-legged or deer tick (*Ixodes scapularis*) is responsible for transmitting Lyme disease in the northeast, mid-Atlantic, and north-central United States. Image credit: Shutterstock/Steven Ellingson.

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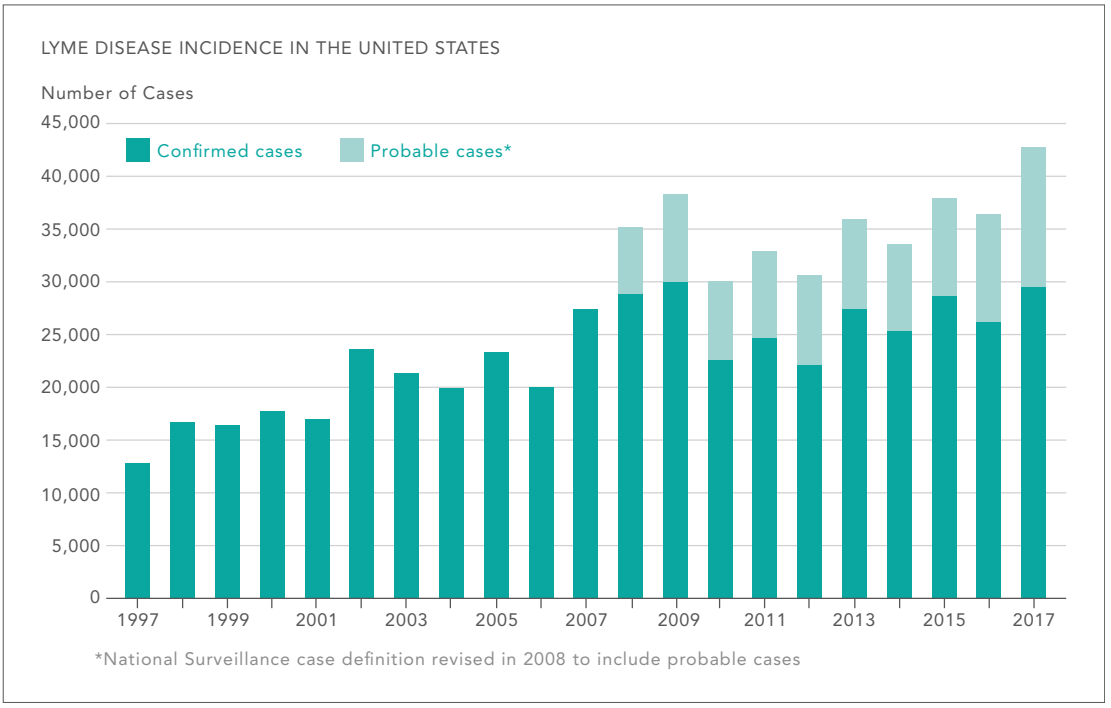

Lyme disease cases have risen steadily in the United States over the past 20 years. Image credit: Centers for Disease Control and Prevention and Lucy Reading-Ikkanda (artist).

No doubt, concerns about the original vaccine are something drug developers and public health officials will have to grapple with as new vaccines strive for success. But although fears related to the original Lyme disease vaccine haven't gone away, the science of vaccine development has changed significantly. Researchers are counting on that new science to put some of those fears to rest.

Still, despite ample promise—Valneva's vaccine has obtained fast-track status from the US Food and Drug Administration (FDA)—there's no way to know for sure what sort of reception these new vaccines will receive from the public. "There will be one more shot at bringing a human Lyme vaccine to market," says Marconi, "and if that vaccine fails, the market will essentially disappear."

First Try

In the late 1990s, the first Lyme disease vaccine came about during a "perfect storm" of adverse circumstances, says Poland, who's also worked as a consultant for Valneva on two occasions. "Around that time, we begin to see just generally, a growing amount of anti-vaccine sentiment," he says.

But anti-vaxxers aside, LYMErix was not a smashing success (1). The vaccine was only 80% effective at preventing the disease, and public health officials had no data on the effectiveness or safety of the vaccine for those under age 15 years, a cohort more at risk of developing Lyme disease because of outdoor play. Plus, it took three doses within two tick seasons to be effective, and intermittent boosters were, by all indications, going to be necessary, says Poland, because of the way the vaccine targets *Borrelia*.

The vaccine worked by inducing antibodies to outer surface protein A (OspA), which is expressed on the surface of the different strains of *Borrelia*. But *Borrelia* only exposes OspA when still inside the tick. When a tick takes in a vaccinated host's blood, the antibodies in that blood can identify OspA and kill the pathogen.

However, if enough *Borrelia* makes it into a host, the bacteria essentially stops expressing those crucial OspA proteins. Hence, for an OspA vaccine to work, the person vaccinated has to produce enough antibodies to block transmission of the bacteria into the host—and that means many booster shots could be necessary (2).

Another strike against the vaccine: the public health agency responsible for recommending its use issued an ambiguous recommendation, saying that people "can use" the vaccine, rather than "must use," says Poland.

But the biggest roadblock stemmed from concerns that the vaccine caused an autoimmune reaction in some vaccine recipients. The vaccine targeted a part of an antigen called the epitope, the section of the protein an antibody attaches to. Some researchers posited that this particular epitope resembled one found on human cells, which would then be attacked by antibodies, causing an arthritis-like reaction in the body (3). Others found a certain genotype could be associated with greater risk of both chronic Lyme disease symptoms and more risk of autoimmune reactions to the vaccine.

Although further review by the FDA and researchers found no connection between the vaccine and such adverse effects, the panel wanted to increase the number of enrollees for the phase 4 (aftermarket) safety

trials. However, those results never came to light: with class-action lawsuits emerging from patients and dwindling market interest, LYMErix was removed from the market in 2002. And with market prospects dim, manufacturer Pasteur Mérieux Connaught dropped a separate, second vaccine, called ImuLyme, that had been in the works. Other companies, including Gaithersburg, MD-based MedImmune, have also tried and failed to get a vaccine off the ground.

Today, two main research strategies are targeting the bacteria that causes Lyme disease: one that continues to focus on OspA and another targeting a different outer surface protein. Each takes a different approach in hopes of avoiding the mistakes of the past.

New Candidates

Valneva is testing an OspA vaccine that is effective against six different subspecies (4) of *Borrelia* found in the United States and Europe, an improvement from the previous vaccine, which only worked on one serotype, *Borrelia burgdorferi*. Safety trials have also recruited people older than age two years, suggesting this vaccine could potentially be used in children. Although it targets the same outer surface proteins as the original Lyme disease vaccine, Valneva's candidate does not make use of the epitope that was associated with purported autoimmune reactions, notes Valneva Chief Executive Officer Thomas Lingelbach. Instead, the researchers combined portions of different epitopes to target a variety of Borrelia strains. Lingelbach makes a point of noting that LYMErix was proven to be safe. Nevertheless, Valneva researchers decided to eliminate its epitope from their antigen to "not give any room to scientific speculation."

"There will be people who will be convinced by data. Then there will be others who will never be convinced."
—Thomas Lingelbach

But as with LYMErix, targeting OspA antigens means producing enough antibodies to stop pathogen transmission. Once inside the host, *Borrelia* switches outer surface proteins and would, therefore, slip by antibodies seeking OspA. Hence, researchers are testing the highest safe dose in clinical trials as they try to reduce the need for yearly booster shots. The goal is to deliver primary immunization over three doses and require a booster shot a year later that remains effective for another three years.

Patient groups may take more convincing. Ten percent to 20% of those diagnosed with Lyme disease deal with recurring symptoms, called chronic Lyme disease. And that constellation of chronic neurological symptoms is similar to what many patient advocates believe are the side effects of the previous Lyme disease vaccine. Pat Smith, president of the Lyme Disease Association, says any new vaccine manufacturer will first need to clarify what went wrong with the previous vaccine. "We need to see what happened, what really happened with LYMErix, and it needs to be done in a transparent fashion," she says.

To address these concerns and make a more effective vaccine, Marconi and his colleagues have targeted an entirely different Osp—OspC. This obviates any need for the much-maligned OspA epitope while delivering immunity with fewer booster shots.

Unlike OspA, OspC is expressed once the bacteria enter the host bloodstream, meaning antibodies will continue to attack the bacteria in the human host, says Marconi. This could mean fewer booster shots; fewer circulating antibodies would be required to strike the bacteria before it transfers out of the tick. However, previous attempts at making an OspC vaccine proved challenging; the protein is highly variable, meaning it might protect against only one particular strain of *Borrelia*, says Marconi.

Marconi and his colleagues studied the variable epitopes of OspC that trigger a productive antibody response. Then, they combined those variations of epitopes into one single protein. They call it a chimeritope. This became a core component of a canine vaccine, called Vanguard crLyme, that the FDA approved in 2016. In that vaccine, both OspC and OspA antibodies work in concert to kill bacteria both inside and outside the tick (5).

In developing a vaccine for humans, Marconi wants to identify new antigens that will play the same role as OspA. Anticipating better acceptance of such a vaccine because of its track record in pets, Marconi says his group hopes to place its vaccine into phase 1 trials in the next few years.

Ideal Target

The ideal strategy, however, wouldn't target bacteria or viruses but the tick itself. Such a vaccine would target proteins in the tick's saliva or midgut to impair tick feeding before the parasite can transmit Lyme disease or any pathogen. In one study, researchers were able to lower transmission of *Borrelia* by vaccinating mice against a protein found in tick saliva and the gut, called tick histamine release factor (6).

A European academic consortium, known as the Anti-tick Vaccines to Prevent Tick-borne Diseases in Europe (ANTIDotE), is wrapping up a five-year project to identify tick proteins that could serve as vaccine targets to impair tick feeding or pathogen transmission or both, notes Joppe Hovius, the project coordinator. "We looked at proteins that could be involved in the transmission of multiple tick-borne pathogens," he says (7).

To narrow the list of potential antigens, researchers used animal models to gauge how developing antibodies to these proteins would hinder tick feeding. Consortium researchers narrowed their candidate proteins to a "few promising results" that impede Lyme disease transmission and tick-borne encephalitis, Hovius says. The results of these experiments are not yet published; Hovius and his team hope to replicate their work as they seek more funding.

The big challenge so far is the genetic diversity among tick populations. One tick saliva protein may not be applicable to others. But if the researchers can find a widely conserved tick protein, they could

potentially target the tick species in both Europe and the United States with one vaccine.

All of these advances look promising, and a better vaccine, whatever the approach, may be within reach. But the challenges of widespread acceptance still cast a pall on the field. Patient groups may have helped thwart LYMErix with public criticism, but, Smith says, "the failure of that vaccine occurred because it was so problematic, and that issue was not really addressed." Clarifying the improvements inherent in new strategies will be crucial, she says.

It remains unclear how Valneva will address past failures if, in fact, the company brings a vaccine to market. With the vaccine still in safety trials, Lingelbach says it's too early to consider what a marketing plan might look like. He does expect more acceptance of a Lyme disease vaccine in Europe because they've already been using a vaccine for tick-borne encephalitis virus for more than 40 years. By the time the company seeks a license for its vaccine, some 16,000 to 18,000 people will have been tested with their candidate, he adds.

But Lingelbach acknowledges the uphill battle. "There will be people who will be convinced by data," he says. "Then there will be others who will never be convinced."

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