

# Q&A: The case of the missing Lyme vaccine

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High summer is here, but many heading to forests and fields reach not for shorts and a T-shirt, but long sleeves, pants, and a shot of bug spray, hoping to keep a threat at bay: the deer ticks that carry Lyme disease.

*Borrelia burgdorferi*, the Lyme disease-causing bacterium transmitted by

[tick bites](#), has been found in increasing numbers around the country, particularly in the Northeast. Early symptoms may include an expanding skin lesion at the site of the bite, often accompanied by fever, headache, and fatigue.

Left untreated, it may attack the joints, heart, and [nervous system](#) with potentially long-lasting impacts, including arthritis, heart palpitations, dizziness, or shooting pains.

Though the threat has grown and become more well-known, there are currently no vaccines for humans, although there are three for dogs. One had been developed in the late 1990s and was pulled off the market in 2002, in part due to a vigorous anti-vaccination movement. The Gazette spoke with Allen Steere, a professor of medicine at Massachusetts General Hospital and Harvard Medical School and a discoverer of Lyme disease, about the prospects for a new vaccine being developed by Pfizer and Valneva, currently in Phase 3 trials.

## **GAZETTE: There are Lyme disease vaccines available for dogs but none for people, even though a human vaccine was developed decades ago. What happened to it?**

Steere: I had a role in evaluating that. I was principal investigator of the Phase 3 trial of the SmithKline Beecham vaccine, the first commercially available vaccine for Lyme disease. That trial involved 10,000 people, 5,000 of whom—I'm giving rough numbers now—received the vaccine and 5,000 of whom received placebo. The single most important factor leading to the withdrawal of the vaccine was a strong anti-vaccine movement.

Some people felt that the vaccine made their post-treatment

symptomatology worse. This was 20 to 25 years ago, and we did not know as much about Lyme disease as we know now. Studies that had been done of patients with Lyme arthritis showed an association between having an antibody response to the bacteria's outer surface protein A, used in the vaccine, and developing what we call today post-infectious Lyme arthritis. But association does not prove causation, and the reason for the association was not altogether clear.

Studies suggested that there was molecular mimicry—partial sequence homology—between outer surface protein A (OspA) of the spirochete and a host protein called LFA-1, and it was proposed that this was perhaps the reason for post-infectious antibiotic refractory Lyme arthritis. The article suggesting that came out in *Science* the same week that the *New England Journal of Medicine* article was published with the results of the Phase 3 vaccine trial. This became a justification for the idea that the vaccine could make your Lyme disease worse.

However, that was shown not to be the mechanism. The reason for the association is that an immune response to OspA in the infection can be a part of an excessive inflammatory response that may set the stage for the development of autoimmune phenomena. However, vaccination alone to a single protein—OspA—does not induce this response. In other words, vaccination was not shown to be a problem.

## **GAZETTE: Is that why we've had to wait decades? There's a candidate in Phase 3 trials now?**

Steere: The vaccine that is being tested now is very similar to the one that was commercially available 20 to 25 years ago. However, the particular sequence that had partial sequence homology with LFA-1 has been removed from the recombinant protein in the current vaccine.

**GAZETTE: So, the mechanism in that original vaccine that supposedly caused problems is not in this new vaccine?**

Steere: That is true. Still, it remains a question how well the new vaccine will be accepted. There are many more cases of Lyme disease, and many more people are aware of the risk of this infection. There are many more places that have become hyperendemic in New England and in the mid-Atlantic states. So, the need for a vaccine has increased a great deal. There's a better understanding of the infection than 20 and 30 years ago. Thus, I expect that the vaccine will be better accepted now. However, other factors are important.

We saw with COVID that acceptance of vaccination is problematic and could be better understood in sociopolitical terms. With an infection that is transmitted person to person, one needs to induce "herd immunity." That is not the case with a tick-borne infection. It doesn't matter whether your neighbor has been vaccinated. What matters is whether you are bitten by an infected tick. If one is worried about that and lives in a hyperendemic area, you can choose vaccination. If you don't want to, you don't have to, and it doesn't impact your neighbor's risk.

The medical community doesn't have to push vaccination for Lyme disease in the same way as with a person-to-person infection. But it's important for people to know what the risk is in their area, and it's important to understand that the vaccine is safe and efficacious.

**GAZETTE: Is there any reason to think that this new version will be better or worse, from an effectiveness standpoint, than the earlier vaccine?**

Steere: I'm not expecting that. It is very similar to previous vaccines so you have a good idea that it will be a safe and effective vaccine.

**GAZETTE: Are there any potentially problematic aspects surrounding this new vaccine that stand out to you?**

Steere: One thing that did not get worked out, because the old vaccine was removed from the market, was what's needed in terms of boosters. This is not a vaccine that you take once and that's all you need. It requires having high antibody titers [concentrations] to the spirochete's (a spiral shaped bacteria) outer surface protein A. Antibody levels have to be high for it to be effective and antibody titers decline after vaccination. This will require boosters, but how often is not known. Also, there is strain variation with *Borrelia burgdorferi*, the Lyme disease agent. There are strains that are more inflammatory and cause more severe disease. We happen to have such a strain in New England, so the risk from that standpoint is particularly great where we are.

**GAZETTE: There's also an mRNA vaccine in the works?**

Steere: Things have changed since 25 and 30 years ago. Lyme disease is not the only tick-borne infection that is a risk factor now. We're aware of six infectious agents transmitted by the same tick. They're not as common as the Lyme disease agent, but it's becoming more so. Anaplasmosis, babesiosis, *Borrelia miyamotoi*, and particularly problematic is the Powassan (deer tick) encephalitis virus: These are potential infections as well and vaccination for Lyme disease does not protect against them. Dr. Tony Fauci, formerly director of the NIH's Institute for Infectious and Allergic Diseases, has called for the development of vaccines against all of these agents.

Erol Fikrig at Yale is trying to understand tick immunity as well as immunity to an infectious agent. What is observed in animals, and in humans to some degree, is that if they're bitten by the same type of tick multiple times, they will eventually develop an inflammatory response to a tick protein—or proteins—that will interfere with the tick being able to feed. And it will fall off. That's nature's way of protecting against ticks.

It's been a difficult problem to figure out but may be an important advance that's in the pipeline. It could potentially protect against all of these tick-borne diseases as opposed to just Lyme disease. And yes, there have already been animal studies published of an mRNA vaccine for Lyme disease, which would be a different way of going about this.

### **GAZETTE: Looking ahead, might the past debate about vaccines for COVID help the introduction of this new Lyme vaccine?**

Steere: I would think so. COVID has certainly brought to the fore the problem of post-infectious syndromes. They are real. We don't understand them well. We don't have good treatments for them. So that is better understood now. It's certainly understood that the infection is spreading a great deal and the need for the [vaccine](#) is more evident now. And with COVID, there has been a regular message to the population that vaccination is a good thing.

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