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Lyme disease vaccination: are we ready to try again?

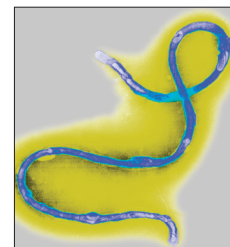
Borrelia burgdorferi—the spirochete that causes Lyme disease—was first identified in 1981. By 1983, it was known that most patients with Lyme disease have antibodies to a 31 kD protein that would come to be known as outer surface protein A (OspA).¹ Antibodies against OspA were shown to protect laboratory animals against experimental infection with *B burgdorferi*.² Research in the 1990s^{3,4} ultimately confirmed the suitability of OspA vaccination for prevention of human Lyme disease. Two commercial OspA vaccines, LYMERix (SmithKline Beecham) and ImuLyme (Connaught) were registered with the US Food and Drug Administration (FDA), and LYMERix was ultimately licensed in December, 1998. Three doses of this vaccine had 76% protective efficacy against definite Lyme disease and 100% against asymptomatic infection.⁴ According to several models,^{5–7} the vaccine was cost effective for individuals at high risk of infection. However, in early 2002, LYMERix was voluntarily withdrawn from the market, merely 38 months after its approval. The withdrawal was not because of any substantiated concerns about safety—the vaccine was not a commercial success.

LYMERix consisted of monovalent OspA from one strain of *B burgdorferi sensu stricto*. However, naturally occurring OspA is antigenically diverse, particularly in Europe and Asia, where the *B burgdorferi* genospecies that cause Lyme disease are much more diverse than are those in North America. Therefore, although LYMERix was effective for Lyme disease in North America, it might not have been suitable in Europe. In *The Lancet Infectious Diseases*, Nina Wressnigg and colleagues address this issue in a phase 1/2 trial of a novel multivalent OspA vaccine.⁸ The vaccine contains epitopes from six distinct

OspA serotypes. In addition to *B burgdorferi sensu stricto*, the vaccine extends coverage to *Borrelia garinii*, *Borrelia afzelii*, and *Borrelia bavariensis*. Wressnigg and colleagues⁸ showed that 30 μ g, 60 μ g, and 90 μ g doses of adjuvanted or non-adjuvanted vaccine induced substantial mean IgG antibody titres against six OspA serotypes after three initial vaccinations (range 6944–17321), and again after a booster given 9–12 months after the first vaccination (19056–32824).

If this new OspA vaccine comes into clinical use, it could prevent Lyme disease throughout Asia, Europe, and North America, where hundreds of thousands of people are infected annually. However, our past experience with Lyme disease vaccination should prompt some circumspection about whether a new vaccine can ever overcome the factors that caused the commercial failure of LYMERix. First, Lyme disease is geographically confined,⁹ and the risk of Lyme disease is related to activities in tick habitat, so not all individuals in regions where the disease is endemic are at equal risk. Second, the disease is not lethal and does not cause permanent morbidity, and outcomes of antibiotic treatment are excellent in most cases.¹⁰ Finally, small rodents are the natural reservoir for *B burgdorferi*, and transmission between people does not occur, so even 100% vaccine uptake would not result in so-called herd immunity. These issues ultimately led to a lukewarm FDA approval for LYMERix and a soft recommendation from the US Advisory Committee on Immunization Practices.^{11,12} Additionally, largely unsubstantiated safety concerns proved awkward for the manufacturer.

It could be too early to judge how Lyme disease vaccination would fare in a European market, but the



Tina Canavali/Visuals Unlimited, Inc./SP

Published Online
May 10, 2013
[http://dx.doi.org/10.1016/S1473-3099\(13\)70085-9](http://dx.doi.org/10.1016/S1473-3099(13)70085-9)
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tick-borne encephalitis vaccine should offer some perspective. Tick-borne encephalitis is transmitted by the same *Ixodes* spp ticks as Eurasian Lyme disease and largely shares its geographical range.¹³ The disease is potentially lethal, leaves many survivors with permanent neurological impairment, and is untreatable. Its vaccine is highly effective and produces sustained immunity.¹⁴ Yet—except in the setting of mass vaccination campaigns, such as in Austria—vaccination frequency in endemic areas of Europe is appallingly low: less than 15% in much of Europe and less than 5% in Slovenia, where the disease is highly endemic.^{15,16}

On one hand, the situation for the tick-borne encephalitis vaccine portends poor uptake of a Lyme disease vaccine in Europe. On the other hand, vaccines for international travellers (eg, for Japanese encephalitis, yellow fever, and typhoid) and the largely occupational vaccine for rabies show that manufacturers can sustain production of vaccines marketed to fairly small risk groups. These vaccines might serve as a good model for Lyme disease. The market for Lyme disease vaccination would probably be larger than the domestic markets for those for travel or occupational purposes. After more than a decade, perhaps we are ready to try again.

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I declare that I have no conflicts of interest.

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Decentralisation of multidrug-resistant-tuberculosis care and management

Published Online

June 4, 2013

[http://dx.doi.org/10.1016/S1473-3099\(13\)70151-8](http://dx.doi.org/10.1016/S1473-3099(13)70151-8)

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Multidrug-resistant (MDR) tuberculosis is an important medical and public health challenge, afflicting an estimated 500 000 new patients each year. Recent progress in the development of new molecular diagnostic techniques¹ and the first new antituberculosis drug registration in almost 40 years² provide reasons for optimism, but still, globally, less than 10% of individuals with MDR-tuberculosis receive treatment of known quality.

Country data for detection and enrolment onto treatment reported to WHO over the past 3 years

paint a varied picture of progress.³ Some high burden countries report steady increases in the numbers of patients treated over the past 3 years, notably India, Russia, and South Africa. However, less than a quarter of the countries providing complete data showed a linear increase in case detection, and less than half showed a year-on-year increase in the numbers of patients enrolled onto treatment. No country that treated more than 500 patients achieved a treatment success rate of greater than 55%. There has been progress in places, but not nearly enough.