intervene early to improve or maintain those patients' health. The availability of vast amounts of digitized data from medical records and other sources creates new opportunities to perfect such methods, but the work has barely begun.

Furthermore, even the most promising models of care for this patient population are far from perfect and need to be evaluated and improved as they are implemented more widely in varied settings. And even when financial incentives are better aligned, the organizational, professional, and management challenges of bringing effective models to scale will warrant greater attention. Novel incentive schemes under the ACA, MACRA, and other initiatives are themselves experimental and will require evaluation and refinement.

*An audio interview with Dr. Blumenthal is available at NEJM.org*

Higher-quality, more affordable care for HNHC patients will require new levels of collaboration among health care providers, payers, communities, social service organizations, academics, researchers, and others. Our five foundations will work together to improve our nation's capabilities in all three of the vital areas noted above: clarifying the needs of HNHC patients, elucidating the best ways of caring for them, and assisting with the spread of proven approaches. We welcome the involvement and support of all stakeholders seeking to improve the performance of our health system by ensuring better care for this vital and growing population.

Disclosure forms provided by the authors are available at NEJM.org.

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# Need for a New Lyme Disease Vaccine

Stanley A. Plotkin, M.D.

The worst recent failure to use an effective vaccine, in my view, has been the lack of prophylaxis against Lyme disease, although the low rate of complete vaccination against the human papillomaviruses is also in competition for this dubious honor. The Centers for Disease Control and Prevention (CDC) has acknowledged the high prevalence of Lyme disease, which it now estimates to be 300,000 cases in the United States, and entomologists have confirmed the geographic spread in the United States of ticks that carry *Borrelia burgdorferi*, the causal bacterium.

It may be argued that simple measures are available to prevent Lyme disease, such as wearing protective clothing and using tick repellents to prevent tick bites to begin with, as well as alert observation for rapid identification and treatment of rashes that are characteristic of borrelia infection. Unfortunately, these measures have low success rates, particularly in children. Measures to control the presence of ticks and to immunize against tick salivary proteins might also help, although immunization against tick proteins is still experimental.

The efficacy of nonvaccine measures to reduce the risk of Lyme disease is questionable, although reduction of tick carriage in mice and deer would materially reduce the risk for humans. Moreover, the nymphal form of the tick is tiny and easily missed. And delays in identifying Lyme disease may open the door to complications including carditis, arthritis, meningitis, facial palsy, and myalgia.

Ironically, two vaccines against *B. burgdorferi* were developed in the 1990s, and both were shown to have high efficacy, although booster doses probably would have been necessary for prolonged protection. Those vaccines were based on the OspA protein of the bacteria; antibodies against OspA pre-

vent replication of the organism in the tick, which then cannot inject borrelia into humans. However, one of the vaccines was not pursued as far as licensure, and the other was briefly on the market before being pulled by the manufacturer because of a lack of demand, caused by weak recommendations by the CDC, poor education of physicians by the manufacturer, and lawsuits by Lyme disease activists, who believed that the vaccine caused significant adverse reactions.

In the safety data obtained during the phase 3 trials of the latter vaccine, there was a signal that transient arthralgia occurred at a higher rate in vaccinees. Although there was no increase in the risk of arthritis in participants who had previously had Lyme disease, which would be expected if sensitization to OspA were a precipitating factor, the observation convinced Lyme disease activists to oppose the vaccine. In addition, the findings of an early immunologic study in hamsters were consistent with the possibility of sensitization, and there was some suggestion that an epitope of OspA was homologous to an epitope of the human Ifa-1 protein. Nevertheless, further studies by the same scientific group and other studies in dogs and humans failed to confirm this hypothetical risk, and a Food and Drug Administration panel concluded that there was no evidence of an association between vaccination and arthritis.

In subsequent years, the problem of Lyme disease has grown. In addition to the estimated 300,000 cases of Lyme disease in the United States, the disease is common in Central Europe, where there are at least 65,000 cases per year.[1] The species of borrelia that infect people in Europe, however, are different from those in the United States. Whereas *B. burgdorferi* (OspA serotype 1) is the major cause in the United States, three other species predominate in Europe: *B. afzelii* (serotype 2), *B. garinii* (serotypes 3, 5, 6, and 7), and *B. bavariensis* (serotype 4). Thus, a vaccine for worldwide use should immunize against multiple serotypes, although a satisfactory vaccine against only serotype 1 would be usable in the United States (though the recent discovery of *B. mayonii* as a cause of Lyme disease in this country may necessitate inclusion of additional antigens).

***The target is a Lyme disease vaccine that prevents strains prevalent on both sides of the Atlantic, is well tolerated, lacks epitopes that would hypothetically cross-react with human proteins, is licensed for use in children, and provides at least 80% efficacy for 2 years.***

The age distribution of Lyme disease in the United States shows peaks in adolescence and an increasing incidence with age, probably reflecting the likelihood of engagement in outdoor activities including camping and gardening. The risk varies geographically: most cases occur in the East between Maine and North Carolina or in the Midwest states of Minnesota and Wisconsin, with scattered cases in the central and far western states. Large numbers of people live in these areas.

Fortunately, scientists have continued to be interested in the prevention of Lyme disease. Several groups have developed candidate vaccines with wider antigenic content. Baxter Laboratories developed a vaccine candidate in which the LA-2 parts of two OspA molecules were fused to make three separate antigens: serotypes 1 and 2, serotypes 3 and 4, and serotypes 5 and 6.[2] Such an approach would target both the U.S. and the European strains of borrelia. To avoid controversy, an LFA-1–like epitope that some experts thought might cause autoimmune responses was removed. Unfortunately, Baxter is no longer developing this vaccine.

However, Valneva, based in Vienna, has produced an OspA vaccine aimed against all six serotypes, based on three heterodimers of the LA-2 epitopes but without the hLFA-1 epitope.[3] The company has announced its plan to test the vaccine in both Europe and the United States. Another approach to a vaccine is based on the mutated C-terminal of OspA.[4] Finally, multiple non-OspA antigens — most notably, OspC — have been shown to protect against borrelia infection by active and passive immunization.[5] Tick salivary antigens are also interesting as potential vaccines, inasmuch as pathogens other than borrelia are injected by ticks. The addition of other antigens might strengthen and prolong protection by OspA vaccines.

Thus, the future seems reasonably bright for the development of vaccines against Lyme disease, if the mistakes made with the

last vaccine can be avoided. In my view, the target product profile is of a vaccine that prevents strains prevalent on both sides of the Atlantic, is well tolerated, lacks any epitopes that would hypothetically cross-react with human proteins, is licensed for use in children, and provides at least 80% efficacy for 2 years. To promote the licensure of a new vaccine against Lyme disease, perhaps the greatest need is a concerted demand by the public health community, which would convince manufacturers that there is a market for such a vaccine.

Disclosure forms provided by the author are available at NEJM.org.

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# Scrub Typhus — Scientific Neglect, Ever-Widening Impact

David H. Walker, M.D.

Scrub typhus, a systemic, life-threatening disease with an enormous incidence in Asia and the islands of the Pacific and Indian Oceans, remains remarkably neglected. Discovery of this vectorborne infectious disease on Chiloé Island in Chile (see report by Weitzel et al., pages 954–61) and its detection in Africa highlight the fact that we have heretofore paid too little attention to it and developed too little relevant expertise.[1] The Allied armies were caught flat-footed during World War II when 18,000 of their troops became ill with scrub typhus in the Pacific theater, and the disease remained a major cause of severe, undifferentiated febrile illness in U.S. military forces in Vietnam. Currently, there is a tremendous widespread reemergence of scrub typhus in locations such as India, Micronesia, and the Maldives, where it had been forgotten, and its incidence is growing in locations such as South Korea and China north of the Yangtze River, where it was previously unknown.

Infection with *Orientia tsutsugamushi*, the causal agent, classically begins with the appearance of an eschar at the site of mite feeding and enlargement of the draining lymph nodes, followed by fever, headache, myalgia, and gastrointestinal symptoms. In severe cases, the illness can progress to the development of interstitial pneumonia, acute respiratory distress syndrome, meningoencephalitis, acute kidney injury, or disseminated intravascular coagulation, causing death in 7% or more of patients unless they are treated sufficiently early in the course of illness with doxycycline, azithromycin, or somewhat less effectively, chloramphenicol.

*O. tsutsugamushi* is an obligately intracellular bacterium that is maintained in nature transovarially in mites. Scrub typhus was named for the scrub vegetation of secondary tropical growth where mature forest had been cut — habitats that provide a favorable environment for rodents, which are hosts to the stage of trombiculid mite that is a reservoir and vector for *O. tsutsugamushi*. The infected larval mite that hatches from an infected egg is the only parasitic stage that feeds on a vertebrate animal such as a human or rodent, which are only incidental hosts. The nymphal and adult mites reside in the soil. Thus, it is impossible to eradicate *O. tsutsugamushi* from its natural cycle with any strategy currently available.

It's essential to understand that the mite is both the vector and the reservoir. Rodents become infected with *O. tsutsugamushi* and maintain the infection for a prolonged period. Then chiggers can become infected by feeding on an infected rodent, but these do not transmit *O. tsutsugamushi* to their offspring transovarially, so chigger–rodent transmission does not represent a vector–vertebrate-host cycle.

Virologists, bacteriologists, and malariologists seldom investigate rickettsial diseases, even though studies of febrile patients in Asia reveal that scrub typhus and murine typhus are often at least as