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January 24, 2001

FEDERAL EXPRESS

Ms. Nancy T. Cherry
Scientific Advisors & Consultants Staff
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Re: **Submission for January 31, 2001 Advisory Committee Meeting**

Dear Ms. Cherry:

As we discussed, please find enclosed our written submission for the Vaccines and Related Biological Products Advisory Committee's January 31, 2001 meeting. We appreciate your distribution of this submission to the Committee members, and we look forward to addressing the Committee at the meeting.

If you require any further information, please do not hesitate to contact me.

Respectfully submitted,

ALBERT J. BROOKS, JR.

Enclosure

REPORT ON LYMErix

Prepared by:
SHELLER, LUDWIG & BADEY
Stephen A. Sheller, Esquire
Albert J. Brooks, Jr., Esquire

Submitted to:
VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE
Advisory Committee Meeting: 1/31/01

I. INTRODUCTION

When SmithKline Beecham's lyme disease vaccine, LYMErix, was last before the FDA's Center for Biologics Evaluation and Research's Vaccine and Related Biological Products Advisory Committee for a vote on its recommendations on May 26, 1998, a great deal of concern was voiced by committee members about both the safety and efficacy of the vaccine, with many members of the Committee left unsatisfied by the results of SmithKline Beecham's human trials.

The Committee ultimately voted to approve LYMErix, but only with "great ambivalence" and "with a stack of provisos".

Over the past two years, we have personally seen the manifestation, in human terms, of the "theoretical" concerns and risks raised by the Committee during that approval. We have been contacted, on an unsolicited basis, by nearly two hundred individuals who believe they have experienced adverse reactions after being vaccinated with LYMErix. To date, one hundred and twenty one (121) of those individuals have retained us to investigate these reactions. It must be noted that these individuals have been unsolicited, and therefore must represent only a small fraction of the adverse reactions actually being experienced. We continue to be contacted by, on average, between five and ten new people each week who report adverse reactions, including arthritic-like symptoms as well as aggressive Lyme-disease-like symptoms, which occurred after vaccination with LYMErix.

The people who have contacted us were, prior to vaccination with LYMErix, healthy, active and energetic. Indeed, the very reason they sought the LYMErix vaccine was their desire to preserve their healthy, active lifestyle. However, what they experienced was a dramatic degradation of their health and quality of life. As will be described below, these previously healthy individuals are now afflicted with painful, at times debilitating arthritic symptoms, including joint pain and swelling, as well as extremely severe Lyme-disease-like symptoms which have persisted to this day.

We wish to emphasize, however, that we submit this Memorandum not in our capacity as counsel for any of these individuals, but in the public interest so that this Committee can be made aware of the real-world effects of LYMErix.

Since LYMErix was approved by the panel of this Committee in May 1998, additional research has been published which reinforces the risks and concerns raised by that Committee.

We have also found the vaccine being distributed in areas which would not be considered "highly endemic" for Lyme disease, and to individuals who would not be seriously considered at either "high" or even "moderate" risk of contracting Lyme disease.

We believe that the nature and extent of adverse reactions, the ongoing scientific evidence supporting the plausibility of a causal connection between OspA and treatment-resistant

Lyme arthritis, especially in certain genetically susceptible individuals, and the balance of a cost-benefit consideration of LYMErix requires an immediate moratorium on the sale of LYMErix, and we strongly urge the Committee to recommend this step now.

We also urge the Committee, in its consideration of this matter, to review all safety and efficacy data submitted to the FDA by Connaught Laboratories, Inc. in support of its application for its Lyme disease vaccine, ImuLyme.

II. THE ADVISORY COMMITTEE CONCERNS

In accepting the vote of approval on LYMErix, Committee Chairperson Ferrieri voted "yes with great ambivalence" and noted that "this is fairly rare for a vaccine to be voted on with so much ambivalence by everyone with a stack of provisos."

Karen Elkins, Ph.D., from the FDA, began the discussion of LYMErix by acknowledging that "in the literature, an association between anti-OspA immune responses and the development of Lyme arthritis has been noted." However, the clinical trial of LYMErix failed to resolve these very serious concerns, as Dr. Elkins stated "It is not clear what, if any, implications these data, which relate to the natural history of the disease, have for vaccination with OspA itself." This was because "T-cell [auto-immune] responses to LFA-1 [the human antigen which OspA mimics] itself **have not yet been studied**." (Emphasis added). The most that could be said on the topic by Dr. Elkins was that, in the human trials "no **apparent** increase in the frequency of arthritis was noted in vaccinees as compared to placebo recipients."

However, Committee members Kohl and Cole expressed concern "about the two cases of paresthesia, arthritis, and the DR positives." Committee member Cole was further concerned that "I don't think you could say that it is safe for everybody 15 to 70, because that hasn't been proven", including with respect to "former Lyme patients." Similarly, Committee member Fleming complained that he was "left with uncertainties about whether there really are, and maybe these two cases of paresthesia [in DR4+ study participants] that we are seeing are in fact a signal of something that we would have seen if we had been able to follow longer. So I am left with uncertainties in that regard."

Committee member Greenberg expressed concern about the need for booster shots after the initial three dose regimen, and stated "I have even more concern about if the vaccine is going to be delivered on repetitive vaccinations, but I have no data to judge its safety." On that same subject, Committee member Coyle expressed concern that, due to the limited immunity conveyed by LYMErix as studied, the three dose regimen "is not likely to be the way this vaccine is going to be used." Similarly, Committee member Snider expressed concern that "in terms of safety, I think what the committee is saying is we have to worry about a longer period of time than the 20

months of data [from the human trials] we have in front of us."

Committee member Clements-Mann expressed uncertainty about what would happen to people who are HLA-DR4+ and develop infection with Lyme disease after being vaccinated, stating that "that would be another important question to look at in terms of safety."

Committee member Karzon recognized that "the safety issue here seems to me to be very complicated compared to any vaccine I know that has been licensed. And we have unearthed the - - those who did the trial have unearthed some very interesting sinister possibilities that may or may not be real. . . we still don't know theoretically whether arthritis patients will get into more trouble if they are vaccinated or not."

Dr. Karzon added that "another safety issue that is there but is unresolved is the very interesting studies that Dr. Steere did to show what seems to be an autoantibody response. . . . we don't know the final answer to that. We don't know the significance of DR4 in a statistical sense. I see a lot of reasons why we have a lot of unsprung threats." (Emphasis added).

Committee member Breiman expressed concern about "the implications of vaccinating a patient that is currently infected or just has been infected within the last few weeks, which would have been another excluded criteria [from the study]. But given the autoimmune issues and the possibility that there may be sort of antibody bug relationship there that could contribute, that is a concern too."

When the question turned to the safety of LYMErix in individuals with a history of Lyme disease, there were similar reservations.

Committee member Dattwyler felt the issue still "has to be studied very rigorously. Committee member Luft concluded "I don't think we have the numbers to say that there is real safety within that group. It is just too small a group [in the human trials]. I don't think we have the - - so I have some real reservations about using the vaccine in people who have had a prior Lyme disease."

Concerns were also raised about the efficacy of the vaccine as tested. Specifically, Committee member Daum warned that "two doses produced . . . I think fairly minimal efficacy in the first season after the two dose regimen was completed. At least it wouldn't be enough for me as a patient to get excited about taking my chances with ticks. . . The point is that someone is going to start their immunization schedule prior to tick season number one, get the two dose regimen, but really not have that good high efficacy until the third dose comes prior to tick season number two." Similarly, Committee member Greenberg stated that "I would just simply say that as best I know, there is no other vaccine that takes a year to develop real efficacy, and I would recommend to the manufacturers that this is not at all optimal. You are asking somebody to buy into vaccination for a whole year before they get benefit, which is not ideal." Committee member Snider also criticized the first year efficacy of LYMErix: "That one year of not being

protected 50 percent is poor frankly."

Finally Committee member Huang voiced a cautionary note to SmithKline about how this vaccine should be presented to the public, given the numerous and serious concerns raised by the Committee: "I wanted to say that this has been an extraordinarily difficult decision for many of us. . . But if you step back and really look at this particular vaccine, it is something that has an unusual three-shot deal for one season of protection, and it may end up have some long-term sequelae that we now have no ideas about. . . . [T]here is something to worry about. So in looking at this and for what we are getting out of this, I would say that for those who are in the process of developing this vaccine and getting it licensed, not to sell it immediately tomorrow and push it as hard as you can for all the money you can get."

III. ONGOING SCIENTIFIC REVELATIONS

Cross-reactivity between *B. burgdorferi* and self antigens has been suspected to cause chronic neurological disease, [1] as well as treatment resistant Lyme arthritis.[2] Specifically, it has been found that the T cell lines from patients with treatment-resistant Lyme arthritis preferentially recognized *B. burgdorferi* OspA, while patients with treatment-responsive Lyme arthritis rarely recognize the protein.[3] And even more specifically, both HLA-DR4 and IgG reactivity against OspA were found to be associated with treatment-resistant Lyme arthritis.[4]

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[1] Sigal, L.H., *Lyme Disease: a Review of Aspects of its Immunology and Immunopathogenisis.* Annu. Rev. Immunol., 1997. 15:63-92

[2] Gross, D.M., Forsthuber, T., Tary-Lehmann, M., Etling, C., Ito, K., Nagy, Z.A., Field, J.A., Steere, A.C. and Huber, B.T., *Identification of LFA-1 as a Candidate Autoantigen in Treatment-Resistant Lyme Arthritis.* Science, 1998. 281:703-706;

Lengl-Janssen, B., Strauss, A.F., Steere, A.C. and Kamradt, T., *The T-Helper Cell Response in Lyme Arthritis: Differential Recognition of Borrelia burgdorferi Outer Surface Protein A (OspA) in Patients with Treatment-Resistant Lyme or Treatment-Responsive Lyme Arthritis*, J.Exp.Med., 1994. 180:2069-2078.

[3] *Id.*;

Kamradt, T., Lengl-Janssen, B. Strauss, A.F. Bansal, G. And Steere, A.C., *Dominant Recognition of a Borrelia burgdorferi Outer Surface Protein A-peptide by T Helper Cells in Patients with Treatment-Resistant Lyme Arthritis,* Infect.Immun., 1996. 64:1284-1289.

[4] Steere, A.C., Dwyer, E.D. and Winchester, R., *Association of Chronic Lyme Arthritis with HLA-DR4 and HLA-DR2 Alleles*, N.Engl.J.Med., 1990. 323:219-223;

Kalish, R.A., Leong, J.L. and Steere, A.C., *Association of Treatment-Resistant Chronic Lyme Arthritis with HLA-DR4 and Antibody Reactivity to OspA and OspB of Borrelia burgdorferi*, Infect.Immun., 1993. 61:2774-2779.

It has further been shown, in an article published after the Advisory Committee's 1998 meeting, that "during periods of maximal arthritis, the levels of IgG antibody to OspA and OspB, especially to a C-terminal epitope of OspA, correlated directly with the severity and duration of arthritis", that is, "the higher the IgG response to OspA and OspB, the more severe and prolonged the arthritis.[5]

Further research, also published after approval of LYMErix, concluded that "the maximum severity of joint swelling correlated directly with the response to OspA."[6]

Another study published post approval in the Journal INFECTION AND IMMUNITY, in which recombinant OspA was administered to hamsters who were then challenged with *Borrelia burgdorferi*, "confirmed the development of severe destructive arthritis in OspA-vaccinated hamsters challenged with *B. burgdorferi* sensu stricto." The authors concluded "these findings suggest that OspA vaccines must be modified to eliminate potential side effects."[7]

This research, and these concerns have resonated with health agencies both in the United States as well as Canada.

Specifically, the Canadian Advisory Committee Statement of the National Advisory Committee on Immunization entitled "Statement on Immunization for Lyme Disease (ACS-3), *Canada Communicable Disease Report, Vol. 26, (ACS-3), 1 July 2000*, while repeating the reported finding that "the Phase III trial did not detect differences in the incidence of neurologic or rheumatologic disorders between the vaccine recipients and their placebo controls in a 2-year post-treatment observation", nevertheless cautions that:

> Roughly 10% of adults and 5% of children with Lyme arthritis develop chronic inflammatory joint disease that does not respond to therapy directed against *B. burgdorferi*. These individuals are more likely to express certain HLA-DR4 alleles and have high levels of antibody directed against OspA in serum and

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[5] Akin, E., McHugh, G. L., Flavell, R. A., Fikrig, E., and Steere, A.C., *The Immunoglogulin (IgG) Antibody Response to OspA and OspB Correlates with Severe and Prolonged Lyme Arthritis and the IgG Response to P35 Correlates with Mild and Brief Arthritis*, Infect. and Immun., 1999. 67:173-181.

[6] Chen, J., Field, J. A., Glickstein, L., Molloy, P. J., Huber, B. T., and Steere, A. C., *Association of Antibiotic Treatment-Resistant Lyme Arthritis with T Cell Responses to Dominant Epitopes of Outer Surface Protein A of Borrelia burgdorferi*, Arthr. & Rheum., 42: 1813-1822.

[7] Croke, C. L., Munson, E. L., Lovrich, S. D., Christopherson, J. A., Remington, M. C., England, D. M., Callister, S. M., and Schell, R. F., *Occurrence of Severe Destructive Lyme Arthritis in Hamsters Vaccinated with Outer Surface Protein A and Challenged with Borrelia burgdorferi*, Infect. & Immun., 2000. 68:658-663.

synovial fluid. It has been proposed that an autoimmune reaction may develop within the joints of these individuals as a result of molecular mimicry between dominant T cell epitope of OspA and human leukocyte function associated antigen 1 (hLFA-1). Most recently, severe destructive arthritis has been reported in hamsters vaccinated with outer surface protein A and subsequently challenged with *B. burgdorferi*.

(A copy of the Report is attached as Exhibit A).

The State of Minnesota's Health Technology Advisory Committee, in its Statement "New Vaccinations: Lyme Disease, Rotavirus, Hepatitis A and Pneumococcal Disease" gives the following warning:

> While the short term safety of LYMErix was determined to be adequate in the efficacy trial, further research on long term chronic sequella and disease-related events is necessary. One particular concern over the long term safety of the Lyme disease vaccine is the possibility that it may trigger arthritis or paresthesias in genetically prone individuals. Individuals who exhibit the HLA type DR4 genotype (the human leukocyte antigen type DR4) are predisposed to rheumatoid arthritis, which is considered to be an autoimmune disease. Individuals with this genotype are also predisposed to treatment-resistant Lyme arthritis, possibly because the protein hLFA-1 (human leukocyte function associated antigen), which has a high binding affinity to HLA-DR4, has a high homology with OspA. This may result in the anti-OspA antibodies acting as autoantibodies against the hLFA-1 protein when it is presented by HLA-DR4. There are general concerns that this vaccine may result in a "late unanticipated event" and that vaccinees should be followed carefully for at least 5-10 years after vaccination to obtain appropriate data on long term effects.

(A copy of the Statement is Attached as Exhibit B).

Indeed, SmithKline's own "Invitation to Participate" in the Safety/Immunogenicity - 016C study, despite the claim that "there was no evidence that the vaccine recipients developed arthritis more often than the placebo group, warns "However, the theoretical possibility still exists that the vaccine may cause arthritis in certain genetically susceptible individuals." (A copy of this form is attached as Exhibit C). It is important to note that this form was signed by a study participant on November 21, 1998, just over a month before LYMErix went to market in January 1999, without any such caveat.

Finally, an abstract presented at the Annual Meeting of the American College of Rheumatology in Philadelphia on Wednesday, November 1, 2000 entitled "*Delayed and Immediate Rheumatologic Manifestations Associated with Recombinant OspA Vaccine*", Rose, C.D., Fawcett, P. T., and Gibney, K., M., of the Alfred I. DuPont Hospital for Children,

documented two confirmed "arthritogenic, albeit transient, effects of OspA vaccination" as well as two cases which were "likely vaccine induced arthritis" with one of those cases "suggest[ing] either current or past *B. burgdorferi* exposure with disease re-activation induced by the vaccine." (A summary of this abstract is attached as Exhibit D).

If LYMErix is to remain on the market, we believe that it is imperative for the medical community at large, and the general public, to whom LYMErix has been vigorously advertised and promoted, to be made aware of these concerns, and the "possibility" that LYMErix "may cause arthritis in certain genetically susceptible individuals. However, as we are seeing the physical manifestation of this "theoretical possibility", we believe these ongoing concerns justify an immediate moratorium on the sale of LYMErix.

IV. PATIENT COMPLAINTS

As mentioned above, over the last two years, we have been contacted, on an unsolicited basis, by approximately two hundred individuals complaining of adverse reactions to the LYMErix vaccine. At present, one hundred and twenty one of those people have retained us to investigate their potential claims.

We have encouraged all of these people to file reports with the Vaccine Adverse Event Reporting System, and on several occasions we have extended an invitation to the FDA to access and review the medical records and personal information which we have collected on these individuals. To date, no one at FDA has accepted our invitation. Similarly, we would be happy to provide this Committee, under the appropriate confidentiality protections, with medical records and personal information on these individuals.

Our purpose herein is to bring to your attention, in general, some of the troubling issues which we have been seeing in our investigations, with specific examples. These few examples are representative of the circumstances of each and every one of our one hundred and twenty one clients. We believe that this patient population is itself representative of a much larger population of vaccinees who have experienced adverse reactions after vaccination with LYMErix.

A. Failure of Vaccinating Physicians to Recognize Adverse Reactions

We have seen several instances of individuals who exhibit adverse reactions which, although mild, are still unresolved by the time the next vaccination in the series is due. Their vaccinating physicians, mistakenly believing that these mild reactions are normal and expected, proceed to administer the next vaccination which triggers a more severe and prolonged reaction.

An example is [redacted] who was an extremely healthy, active 58 year old woman at the time she received her first vaccination with LYMErix on June 1, 1999. After that shot she experienced mild flu-like symptoms. Thereafter, she was given her 2nd shot on June 30, 1999 and

immediately began experiencing severe flu-like symptoms, which gradually progressed to extreme joint and muscle pain all over her body. —. explains that she feels like she "went from 58 to 85".

By September 1999 — was hospitalized, as she could not move her legs. To this day she continues to find it difficult to function, even on significant doses of Prednisone and anti-inflammatories.

Of note, — was tested and found to be HLA-DR4+.

—. is also an excellent example of the utilization of LYMErix in areas not considered "highly endemic". —. received her vaccinations at her summer residence in Florida, in anticipation of her return to Minnesota. As explained below, neither Florida nor Minnesota can be considered "highly endemic", and do not meet the CDC's own criteria for the cost-effective use of LYMErix.

Another example is — who was 74 at the time of vaccination and had a history of Lyme disease from 1992. Prior to vaccination she was in general good health. After the 1st shot in February 1999 she experienced flu-like symptoms and "flashing lights". Then after the 2nd shot she experienced a "terrible pain", followed shortly thereafter by total paralysis. She was hospitalized on an emergency basis and ultimately diagnosed with "transverse myeolitis." To this day she remains on a feeding tube.

Another case in point is '—, a 38 year old male at the time of his vaccination, whose physician not only failed to recognize his adverse reaction, but also administered the vaccine in an "off-label" schedule[8].

—. received his first vaccination on March 3, 1999. At that time he was healthy and active. Almost immediately after his first shot — experienced severe flu-like symptoms which lasted 3-4 days, and which were recorded by his vaccinating physician on April 13, 1999 as "head cold, lung, nose", and diagnosed as an upper respiratory infection. — received his second shot on April 28, 1999 and the following day experienced extreme pain in his joints and muscles, and became very stiff. He reported this to his vaccinating physician on April 29, 1999, who rendered no diagnosis, but noted a plan for the 3rd vaccination in 6 weeks.

That pain and stiffness left '—. confined to bed for a full week, during which he described himself as being "basically crippled". The following week he could begin to walk a little. When he reported all of this to his physician, and questioned whether he had contracted

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[8] We have seen several cases of physicians administering LYMErix under the mistaken belief that a 0, 1 and 2 month or 0, 1 and 6 month schedule is either approved or recommended. We also have a few cases of physicians administering LYMErix to individuals over seventy (70) years of age.

Lyme disease itself, the vaccinating doctor not only assured him that he had not (without any confirmatory laboratory work), but warned —. that if he did not finish the full schedule of three shots, he might experience adverse reactions.

Accordingly, on June 9, 1999, his symptoms having lessened somewhat —— returned for his 3rd vaccination with LYMErix. By June 16, 1999, all of the symptoms he experienced after the 2nd vaccination had returned, to a greater extent, and have not subsided since.

To this day, over nineteen (19) months after his final vaccination, —. continues to suffer from joint pain, back pain, and headaches to such an extent that he has been forced to stop working.

In some cases, the physician's failure to recognize a complaint as a possible adverse reaction to the vaccine has resulted in what was likely unnecessary surgery. For example, —— was a 55 year old man when he was vaccinated in April and May 1999. He became extremely ill with, among other symptoms, severe joint and back pain. At a physician's recommendation, he underwent surgery to remove his coccyx bone in September 1999. Not only was this surgery ineffective, but it directly resulted in an osteomyeolitis infection.

—— is a 68 year old man who was vaccinated with LYMErix in 1999 and early 2000. Shortly after his final shot he developed such severe pain in his knee joint that he was unable to work. He subsequently underwent exploratory surgery in July of 2000 and was told that he will need knee replacement.

It appears to us that physicians are either uninformed or misinformed about the safety issues related to LYMErix and they fail to recognize the significance of boosting the patient's immune system with such a highly immunogenic agent as ospA either while or after the patient's immune system has already reacted adversely to an initial introduction of ospA. We believe these cases provide evidence that the initial introduction of ospA, with its resulting reaction, "primes" the body for more aggressive reaction to subsequent administrations of either ospA (through vaccination) or OspA (through natural infection).

B. Vaccination triggering prior or current Lyme Disease

Another issue which we have encountered is the vaccination of individuals with a history of Lyme disease, and who almost immediately experience a re-occurrence of their symptomatology.

Probably the most troubling example of this phenomenon which we have seen is —— who was 17 years old at the time of her vaccinations in May and June of 1999. She had a history of a tick bite with bull's eye rash and nausea from 1994 which resolved after 2 weeks of antibiotics.

In June of 1999, after the 2nd injection —— began experiencing joint pain. By October she was experiencing flu-like symptoms with a pinpoint rash on her abdomen. At this time she was also stricken with peripheral blindness in her right eye.

She has not improved despite Prednisone, Rocephin and Celexa. A physician who has evaluated her case opines that "it represents an activation of underlying Lyme disease."

Of note. —— was tested and is HLA-DR+.

Another example is —— a 54 year old woman who was treated for Lyme disease in the Summer of 1998. On March 29, 1999 she was reported to be "100% better, except for some stiffness of the left hand". On that date, she was given her first vaccination with LYMErix, along with a prescription for one month of Celebrex for her continued hand stiffness.

She continued in the same condition until her second shot on April 3, 1999. After that second shot she experienced joint pain, vision impairment, palpitations, chills and a bull's eye rash over the injection site. To this day she continues to experience significant joint pain, stiffness, fatigue, swelling of her hands and an impaired vision field in her left eye.

—— was a 43 year old man with a history of Lyme disease and Babesiosis from July 1998, but was symptom free by October 1998 after one month of antibiotics. In March 1999, his physician began administering LYMErix on an "off-label" schedule of March1, 1999 and March 29, 1999. On April 12, 1999 his Western Blot test revealed IgG band 58, and on April 26, 1999 he was given his 3rd LYMErix vaccination.

Thereafter, he began experiencing severe, pervasive, persistent and acute joint and muscle pain. On June 23, 1999 his Western Blot revealed IgG bands 18, 30 and 58. By January 4, 2000 his Western Blot showed IgG bands 39 and 58 and by April 19, 2000 he was showing IgM band 23 and IgG bands 18, 41 and 58.

We have seen similar reactions, even among individuals with no definite prior diagnosis of Lyme disease.

For example, —— is a lady whose physicians administered LYMErix "off-label" when she was 76 years old, but in otherwise good health. She received the vaccine on May 27, 1999, and shortly thereafter developed a large rash on her stomach, joint pain, fatigue and general flu-like symptoms. She was placed on oral antibiotics starting on June 10, 1999 and ultimately from October 29, 1999 through November 26, 1999 she was administered intravenous antibiotics. The I.V. antibiotics finally relieved many of her symptoms, but to this day she continues to experience joint pain and fatigue.

We have been contacted by other individuals who were actually being treated for Lyme disease at the time they were vaccinated —— . was a 52 year old man whose physician in April

of 2000 noted a tick bite one week prior. The physician prescribed Doxycycline and administered the vaccine. The second vaccination was administered on May 4, 2000. —— reports becoming "like a cripple" with significant joint pain for a short time after the first shot, and again after the second shot. To this day these symptoms have not totally resolved.

—— was a 39 year old male whose physician administered LYMErix on the same day that he was still prescribing Doxycycline for an ongoing Lyme disease infection whose symptoms had basically resolved. —— began experiencing fever, chills and an extremely painful and widespread rash which has not resolved. His differential diagnosis includes "urticarial allergic reaction which is usually a reaction to a drug."

We believe that these cases provide strong evidence that the vaccine causes "flare-ups" of prior infection, and also "primes" the body to suffer a more aggressive form of Lyme disease in the event of a vaccine failure. The close temporal relationship which has been seen, together with the aggressiveness of the flare-ups and their resistance to easy treatment, weighs in favor of warning physicians to refrain from administering LYMErix in individuals who demonstrate any recognized "Lyme-specific" Western Blot bands, such as 34, 39, 41, 47, 58 etc. In fact, we believe that when the CDC's artificially high "two tier reporting criteria" is utilized for diagnostic purposes, it discounts the true number of asymptomatic cases of Lyme disease possibly being activated by vaccination with LYMErix.

C. Acute Onset of Arthritic Symptoms in Otherwise Healthy Individuals

Another category of adverse reaction which we have seen is a series of individuals who are otherwise very healthy, but suffer an acute onset of arthritic-like symptoms shortly after vaccination with LYMErix.

An excellent example of this is —— , who was a healthy 40 year old man when he began his schedule of LYMErix vaccinations in June of 1999. However, by November 1999 he was diagnosed with "oligoarthritis type of symptoms over the last few weeks in his hands, wrists, knees, feet and ankles." By the end of November 1999, his working diagnosis was "polyarticular small and large joint symmetrical synovitis of the upper and lower extremities w/ positive rheumatoid factor - probable new onset rheumatoid arthritis."

Since then —— has been on a significant dosage of Prednisone as well as various anti-inflammatories which have been of very little assistance. He has been unable to fully taper the Prednisone, and was forced to miss four months of work. He continues in pain, and has now been forced to switch to a desk job, from the very active, physical job he enjoyed previously.

—— was a healthy 47 year old man when he received LYMErix on September 22, 1999 and October 22, 1999. By January 2000 he began experiencing severe, joint pain of acute onset which worsened through February 2000. To this date these arthritic-symptoms have not resolved, despite the prescription of Vioxx, Prednisone, Methotrexate, and Plaquenol.

Of note, — . was tested and found to be HLA-DR4+.

— was a healthy 43 year old woman when she received LYMErix in March and May of 1999. After the 2nd vaccination she experienced what she describes as severe disabling joint pain all over her body. This pain then localized in her back, neck, knees, elbows, fingers and jaw. The pain tends to get progressively worse as the day goes on. When it is bad in her knees, she has difficulty walking by the end of the day. On days that the pain strikes her elbows, she has difficulty lifting by day's end. Due to the extreme fatigue she has experienced, her days end by 7 p.m. when she is forced to go to bed, despite being the mother of 12 and 16 year olds.

Of note, — . was found to be HLA-DR4+.

These cases are, perhaps, most ominous because they are similar to the symptoms seen in treatment-resistant Lyme arthritis and late-stage Lyme disease. The extensive research done on that subject by Steere, *et al.* suggests that the condition, while extremely rare when experienced as a result of natural infection, may be auto-immune and extremely difficult to cure.

The risk of such an extremely serious auto-immune disease being triggered by LYMErix is nowhere close to being outweighed by the extraordinarily meager protective benefits conferred by the vaccine, especially in light of the relative ease-of-treatment of Lyme disease when ultimately contracted, as explained below.

D. Inability of Clinical Trial Participants to Report Adverse Reactions

A final phenomenon which we have discovered, and possibly the most troubling, is the difficulty and/or inability of participants in the clinical trials to report post-trial adverse reactions.

Specifically — received the vaccine as part of the LYMErix clinical trial in Rhode Island. He recalls that after the 2nd and 3rd shot, and possibly even after the 1st, he experienced immediate symptoms and pain including headache, neck pain, hip pain, back of left arm and aching muscles and joints, which he says he reported to the study investigator.

At the time, those symptoms were somewhat intermittent. However, he reports that the symptoms increased in frequency and intensity as time went on. The symptoms are now to the point that he is becoming disabled, and he reports that he has been diagnosed with arthritis "throughout" his body.

What is most disturbing is that, after month 20 of the study, he has never been contacted by anyone at SmithKline to follow up on his condition. When he tried to contact the Vaccine Adverse Event Reporting System recently, he was told that they would not accept his report since he was in the study. And rather than direct him back to the manufacturer, or anyone else, he was told that he is "on his own".

— is another individual who participated in the clinical trials in Pennsylvania. He initially received the placebo, but in March and April 1997 he was offered and accepted the vaccine. By November 1997 he was noticing slight pain in his arm joints. He received the 3rd injection in the Spring of 1998 and within a week his symptoms became quite severe, with a burning and cramping in all of his joints, and the sensation of "a hundred razor blades" poking his knee joints, hips, ankles, wrists and elbows.

Most troubling is that when he tried to report this reaction to the medical center that administered the vaccine, he was told "too bad, the study's over, and it's in your body already anyway".

We have heard from other people who, while in the study (as well as the Connaught Laboratories ImuLyme study), brought their complaints to the study-doctor and were told, definitively, that their symptoms could not be related to the vaccine. For example — participated in the clinical trials in 1996 and received the placebo. In 1997 she was offered and accepted the vaccine. During the time in which she was receiving the actual vaccine, she began experiencing arthritic-like joint pain. She reported this to the study-doctor and was told summarily that the shots "had nothing to do with the pain."

We have serious questions about the extent of examination and investigation which was, or was not, undertaken prior to this definitive "diagnosis", as well as the authority of a study-doctor to unilaterally discount a complaint as an adverse reaction. We question whether, having so definitively discounted the complaints, the study-doctors even recorded them. This type of conduct may have contributed to not only the under-reporting of adverse reactions, but to the study participants' reluctance to bring the continuity or progression of the symptoms to the study-doctors' attention, having been so summarily dismissed initially.

In addition to these people, we have heard from other individuals who received the placebo initially and were then offered the vaccine. They began experiencing mild to moderate achiness and joint pain which they did not, at the time, associate with the vaccine. Subsequently that achiness and pain progressively worsened. When they learned from news reports about a possible connection between the vaccine and arthritic-like symptoms, they began to connect their symptoms with their participation in the clinical trials. However at that point they did not know who to contact, and the Vaccine Adverse Event Reporting System was not accepting reports from study participants. As was the case with —. above, VAERS often did not direct them back to the manufacturer, or to anyone else, and their cases have gone unreported.

Finally, we believe that the study's utilization of the CDC "two-tier criteria" for defining Lyme disease had the effect of underestimating the actual number of asymptomatic cases of Lyme disease experienced by participants, both at entry and during the study, and may have skewed the study data with respect to both safety and efficacy. Specifically, utilization of this artificially high criteria made it impossible to distinguish between a vaccine-failure and a vaccine-induced re-activation of prior asymptomatic infection.

While these instances, which came to us unsolicited, are obviously anecdotal, they demonstrate a troubling phenomenon which raises troubling questions about the validity of the safety and efficacy data of the clinical trials. They demonstrate a fundamental flaw at the data entry stage of the study's analysis, which quite probably served to skew the results in the direction of under-reporting adverse reactions.

It also demonstrates the need for a more active, on-going surveillance of study participants by an independent body, especially of the individuals who initially received a placebo and subsequently received the vaccine. At a minimum, these individuals should be contacted and interviewed by an independent, impartial investigator, to determine what if any symptoms they experienced both during and after their participation in the study, and whether those experiences are fully and accurately reported in the clinical study data.

V. RECOMMENDED DIAGNOSTIC TESTS

We believe the body of scientific knowledge, both pre- and post-approval, together with the pattern of adverse reactions, demand diagnostic monitoring of vaccinees and prospective vaccinees.

Specifically, we believe the voluminous research demonstrating the well-established connection between OspA antibodies, treatment-resistant Lyme arthritis, and certain HLA-DR phenotypes recommends screening for the genetic markers in question prior to vaccination with LYMErix, especially if an individual has experienced any degree of adverse reaction to an initial vaccination with OspA.

The issues of LYMErix and prior or current *B. burgdorferi* infections recommend screening for Lyme disease prior to vaccination, with special attention to all "lyme specific" bands rather than the CDC two-tier reporting criteria, again especially for individuals who have experienced any degree of adverse reaction to an initial vaccination with OspA.

Finally, we, believe that those vaccinees who have experienced joint swelling after vaccination with LYMErix should be asked to undergo proliferation assays to determine the T-cell response to various epitopes of OspA containing peptides 9, 15, 21, 24. Studies have shown that such tests reveal significant reactive responses among patients with treatment-resistant Lyme arthritis when compared to patients with treatment-responsive Lyme arthritis.[9] While this was found in proliferation assays performed on peripheral blood, although an even greater magnitude of reactivity was seen with synovial fluid.[10]

In fact, we are aware of at least two individuals who experienced severe joint swelling

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[9] *Id.*

[10] *Id.*

after vaccination with LYMErix and were subsequently referred by their treating physicians to Dr. Allen C. Steere for evaluation. Dr. Steere performed proliferation assays to detect both OspA, OspA: peptide 15 and hLFA-1. However, these assays were performed on peripheral blood despite the fact that the patients presented with extensive joint swelling at the time of their visits.

We do not understand why the assays were not performed upon the patients' readily available synovial fluid, or why Dr. Steere failed to bring the availability of the synovial fluid assay (with its greater diagnostic ability) to the attention of the referring physician when reporting the results of his peripheral bloodwork. Apparently this is because the specific etiology of their joint swelling (i.e. vaccine-induced vs. coincidental development of arthritis) will not effect the treatment plan. Nevertheless, even if such tests do not serve Dr. Steere's immediate purpose in treating these patients, we believe the interest of determining the safety of LYMErix requires such tests, when possible and acceptable to the patient.

We also note that Dr. Steere drew blood for "genetic tests" on these two individuals, which he explained to them was for "research purposes only." At least one of the patients was determined by a subsequent physician to be HLA-DR4+.

It appears from these two patients that Dr. Steere is undertaking research specifically related to the possible connection between the vaccine and joint swelling, especially vis a vis certain genetic susceptibilities. The fact that the lead investigator of the LYMErix clinical trials is continuing to conduct such safety-related studies indicates to us that the outstanding questions regarding the safety of LYMErix justify, at least, enhanced warnings, if not an out-right moratorium.

VI. OVERUSE AND COST/BENEFIT OF LYMErix

In addition, to the concerns noted above, both the Advisory Committee and, subsequently, the Centers For Disease Control, recommended that the vaccine "should be considered" only for individuals in highly endemic areas and at high risk for Lyme disease, with a much more circumspect recommendation for all other individuals.

Indeed, in a May 4, 1999 article in the New York Times, Dr. Allen Steere is reported as having "his doubts about the safety of the vaccine, which he has not taken himself, he said, because Lyme is not a serious problem in the Boston area." And in a speech in California, Dr. Steere asserted that the vaccine is not recommended in non-endemic areas, and "in any site in California that would be the case."

An analysis by CDC indicates that the cost of immunizing with LYMErix exceeds the cost of not immunizing unless the incidence of Lyme disease exceeds 1% per year.[11] However, most endemic states and counties report Lyme disease incidence rates well below 1% per year. In fact, according to CDC's own analysis, between 1989-1998, the State with the highest annual incidence of Lyme disease per 100,000 persons was Connecticut, and its incidence was 54.2 per 100,000. See: *Lyme Disease: Questions and Answers* (posted at www.cdc.gov/ncidod/dvbid/lyme_QA.htm. The next closest states, Rhode Island and New York , reported incidences of 37.5 per 100,000 and 21.6 per 100,000, respectively. *Id.* No other state reported an incidence greater than 16.9 per 100,000 (New Jersey). *Id.*

Indeed, even in endemic areas, the risk of infection with *B. burgdorferi* "is very small, prompt treatment is highly effective, and long term, serious complications are rare." See: *Lyme Disease: Is Vaccination Right for You?,* The Johns Hopkins Medical Letter, April 2000.

We should point out that this cost/benefit analysis is based upon the cost of a three-shot schedule. However, the relatively limited duration of protection afforded by LYMErix means that any meaningful long-term protection would require repeated boosters, perhaps as often as every year. In addition to tilting the cost/benefit analysis further against the cost-effectiveness of vaccination with LYMErix, the need for additional boosters increases, perhaps exponentially, the risks of adverse events associated with high levels of OspA antibodies in the bloodstream.

The limited duration of immunity, if any, which makes these boosters necessary, is not adequately conveyed by either the package insert or the promotional materials which are distributed for LYMErix. Nearly everyone who has contacted us has been given the impression, through the LYMErix promotional materials, that the three-shot schedule will provide them with, at least, long-term protection similar to other vaccines. They are not aware of the limited duration of immunity conferred by LYMErix and universally state that, if they were aware of that limited duration, they would not have chosen to receive the vaccine. The fact that other individuals are similarly not aware of this limited, if any, protection, raises the concern that they may refrain from taking other Lyme disease precautions and consequently increase their risk of exposure to Lyme disease in the future.

Despite these figures, LYMErix has been aggressively marketed in areas which are in no way considered "highly endemic." As just one example, the marketing onslaught in Minnesota prompted the State Department of Health to take note that "the option of getting vaccinated against Lyme disease has received a great deal of attention recently" while "many Minnesotans may have an exaggerated sense of the risk they face from these diseases, based on the false impression that the entire state is a 'hot spot' for Lyme disease. (A copy of this press release is attached as Exhibit E). Actually according to CDC, the annual incidence of Lyme disease in Minnesota between 1989-1998 was only 3.8 per 100,000, well below the 1000 per 100,000

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[11] Meltzer, M. I., Dennis, D. T., Orloski, K. A., *The Cost Effectiveness of Vaccinating Against Lyme Disease*, Emerg.Infect.Dis., 1999; 5:321-328.

necessary to render vaccination cost-effective by the CDC's own analysis.

Finally, a rather common sense refutation to the cost-effectiveness of LYMErix is the well established treatment guideline against prophylactically treating with oral antibiotics upon a tick bite alone. The rationale against the administration of safe, inexpensive oral antibiotics without either clinical or laboratory evidence of infection is the widely accepted notion that such infection is easily and inexpensively treated once detected. It should be obvious that, if the risk of Lyme disease is not substantial enough to justify prophylactic administration of relatively safe and inexpensive antibiotics upon confirmed tick bite, then it certainly does not justify the prophylactic administration of a costly, potentially very harmful vaccine.

It is curious to us that some of the physicians who most adamantly oppose antibiotic-treatment-on-tick-bite most vigorously support the widespread distribution of LYMErix. We find that position to be contradictory and suspect.

VII. CONCLUSION

For the reasons we have set forth above, we strongly urge this Committee to recommend an immediate moratorium and/or withdrawal of LYMErix from the market until safety and efficacy are established by reliable, valid, independent analysis and study.

In the event the Committee is not prepared to take such step at this time, we think that an immediate emergency revision and enhancement of the warning label is mandatory in order to permit physicians and the public to make a truly informed decision about whether to vaccinate with LYMErix, and to better equip the medical community to recognize and respond to adverse reactions which have already, or which may in the future, be caused by the vaccine.

We once again reiterate our invitation to make the medical records and information pertaining to our clients available to the FDA for its review, subject to the appropriate confidentiality protections, and we stand ready and willing to assist this Committee in anyway possible.

Respectfully submitted,

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ALBERT J. BROOKS, JR., ESQUIRE

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Canada Communicable Disease Report Vol. 26 (ACS-3) 1 July 2000

An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)*†

STATEMENT ON IMMUNIZATION FOR LYME DISEASE (ACS-3)

Adobe Downloadable Document PDF (197 KB)

PREAMBLE

The National Advisory Committee on Immunization (NACI) provides Health Canada with ongoing and timely medical, scientific, and public-health advice relating to immunization. Health Canada acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge, and is disseminating this document for information purposes. Persons administering or using the vaccine(s) should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian licensed manufacturer(s) of the vaccine(s). The manufacturer(s) has only sought approval of the vaccine(s) and provided evidence as to its safety and efficacy when used in accordance with the product monograph(s).

INTRODUCTION

Lyme disease is a tick-borne zoonosis caused by infection with the spirochete, *Borrelia burgdorferi*. In the United States, the disease is mostly localized to states in the northeastern, mid-Atlantic, and upper north-central regions, and to several counties in northwestern California. The number of annually reported cases of Lyme disease in the United States has increased about 25-fold since national surveillance began in 1982, and a mean of approximately 12,500 cases were reported annually by states to the United States Centers for Disease Control and Prevention (CDC) from 1993-1997[1-3]. In Canada, only 278 cases that met the Canadian surveillance case definition for Lyme disease were reported to the Laboratory Centre for Disease Control (LCDC) between 1987-1996 (Dr. P. Sockett, Bureau of Infectious Diseases, LCDC, Ottawa: personal communication, 2000). However, Lyme disease was not a reportable illness in all provinces during this period; therefore, this number is likely to be an underestimate. Indeed, between 1984 and 1994, a total of 205 cases of Lyme disease were reported to the Ontario Ministry of Health and less than half of these cases (n = 105) appear to have been acquired locally[4]. Virtually all of the cases reported in other provinces could be epidemiologically linked to travel or exposures in endemic areas of the United States (Dr. P. Sockett, Bureau of Infectious Diseases, LCDC, Ottawa: personal communication, 2000).

Ixodes ticks (the vector) are widely distributed in the southern regions of Canada[5-7] and surveillance in southern Ontario and Quebec has recently demonstrated that a small proportion (< 10%) of these ticks are infected with *Borrelia burgdorferi* (L. Trudel, *Laboratoire de santé publique du Québec*, Ste-Anne de Bellevue, Dr. H. Artsob, Zoonotic Diseases Section, Bureau of Microbiology, LCDC, Winnipeg: personal communications, 2000). At the current time, vector ticks are known to be established in only two localized regions of southern Canada: (1) *Ixodes pacificus* is present in regions of the Fraser delta, the Gulf Islands, and Vancouver Island; and (2) reproducing populations of *I. scapularis* are established along the north shore of Lake Erie (Long Point, Point Pelee, Rondeau Provincial Park)[6]. Although adult vector ticks (occasionally infected with *B. burgdorferi*) have been identified in southern regions of most other provinces, it is highly likely that these isolations represent 'adventitious ticks' carried by migratory birds from endemic areas of the United States[4]. Even in American regions with high transmission rates of Lyme Disease (incidence > 1%), the

disease remains very focal in nature and the risk of infection varies greatly from county to county and even within individual counties[3]. **There are no such regions of high transmission in Canada.**

Lyme disease most often presents with a characteristic rash (erythema migrans), accompanied by nonspecific symptoms such as fever, malaise, fatigue, headache, myalgia, and arthralgia[8-10]. The incubation period from infection to onset of erythema migrans is typically 7 to 14 days, but may be as short as 3 days and as long as 30 days. Erythema migrans is observed in at least 85% of patients with symptomatic infection[8]; however, a small proportion of infected individuals have no recognized illness (asymptomatic infection determined by serologic testing), or manifest only non-specific symptoms such as fever, headache, fatigue, and myalgia. Persons with known exposure in the endemic area and erythema migrans have a high likelihood of Lyme disease[8]. Co-infection with *Babesia* sp. is occasionally reported, as the vector for both organisms is the *Ixodes* tick[7].

Lyme disease spirochetes disseminate from the site of inoculation by cutaneous, lymphatic, and bloodborne routes. The signs of early disseminated infection usually occur days to weeks after the appearance of a solitary erythema migrans lesion. In addition to multiple (secondary) erythema migrans lesions, early disseminated infection may manifest as disease of the nervous system, the musculoskeletal system, or the heart [8-10]. Neurologic manifestations include lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy), and radiculoneuritis. Musculoskeletal manifestations may include migratory joint and muscle pains, with or without objective signs of joint swelling. Cardiac manifestations are rare but may include transient atrioventricular blocks of varying degree.

Without treatment, *B. burgdorferi* infection typically progresses to late disseminated disease weeks to months after infection[8-10]. The most common manifestation of late disseminated Lyme disease is intermittent arthritis of one or a few joints – usually large, weight-bearing joints such as the knee. Less frequently, patients develop chronic axonal polyneuropathy or encephalopathy, the latter manifested by subtle cognitive disorders, sleep disturbance, fatigue, and personality changes. Infrequently, Lyme disease morbidity may be severe, chronic, and disabling, especially if the disease is treated late[8-10]. In its early stages, the disease is readily cured with oral antibiotics. However, untreated or inadequately treated infection may progress to late-stage rheumatologic or neurologic complications requiring more intensive therapy. Lyme disease is rarely, if ever, fatal. An ill-defined 'post-Lyme disease syndrome' appears to occur in some individuals following treatment for Lyme disease[10-12].

Most *B. burgdorferi* infections are thought to result from peri-residential exposure to ticks during property maintenance, recreation, and leisure activities in endemic areas[3,13]. Therefore, individuals who live or work in residential areas surrounded by woods or overgrown brush infested by vector ticks are at risk of acquiring Lyme disease. In addition, persons who participate in recreational activities, such as hiking, camping, fishing, and hunting in tick habitat, or engage in outdoor occupations, such as landscaping, brush clearing, forestry, and wildlife and parks management in endemic areas, are at risk of acquiring Lyme disease[3,14].

PERSONAL PROTECTION

The first line of defense against Lyme disease and other tick-borne illnesses includes the avoidance of tick-infested habitats, use of personal protective measures, such as repellents and protective clothing, and checking for and removing attached ticks[3,15]. Long sleeved shirts and long pants that are tight at the wrists and ankles (or tucked into work gloves or socks) can act as effective barriers. Light coloured clothing (e.g. shirts, pants, socks) can aid in the detection of ticks that have not yet attached. A hat should be worn in areas where contact with vegetation cannot be avoided (e.g. dense woods, high grasses, or thickets).

Ticks can be deterred to some extent by insect repellents containing N,N-diethyl-m-toluamide (DEET). Although many DEET-containing formulations are available ranging in concentration from 15% to 100%, maximum deterence is achieved with products containing approximately 30% DEET. All such products need to be applied often (every 1 to 2 hours) for optimal efficacy and are less effective with heavy sweating or wetting. Frequent and heavy application of DEET-containing repellents can result in serious neurologic complications in children (e.g. seizures)[16]. Such events are rare however and the risk is low when used according to product label instructions[17]. Repellents should be applied as recommended only to exposed and

intact skin. Specifically, repellents should not be applied to diseased or abraded skin, or to the face and hands of children. Skin should be washed with soap and water as soon as possible after leaving the risk area. Permethrin (a synthetic pyrethroid) is available as a spray in animal care stores for application on clothing and cloth (e.g. tent screens) only. Permethrin kills ticks on contact. Daily inspection for attached tisks is also critically important. Animal studies suggest that transmission of *B. burgdorferi* from infected ticks usually requires at least 24 hours and often as long as 48 hours[18,19]. As a result, daily inspection and prompt removal of ticks can prevent transmission.

Particular attention should be given to children and to exposed, hairy areas of the body where ticks often attach (e.g. head, nape of neck). Ticks should not be squeezed during removal. The preferred technique requires firm application of fine tweezers as close to the skin as possible and removal of the tick straight backwards without rotation. Fingers should not be used to remove ticks. If this is unavoidable, gloves should be worn and/or exposed skin should be washed with soap and water immediately after removal of the tick(s).

PREPARATIONS USED IMMUNIZATION

Two Lyme disease vaccines have recently been developed using recombinant *B. burgdorferi* lipidated outer surface protein A (rOspA) as immunogen (LYMErix™, SmithKline Beecham Pharma; ImuLyme™, Aventis Pasteur Limited). At this time, only LYMErix™ has been licensed by the Health Protection Branch for use in Canada, and this statement applies only to the use of this vaccine. Each dose of this vaccine contains 30 μg of OspA produced in *Escherichia coli* adsorbed onto aluminum hydroxide adjuvant (0.5 mg). Supplemental statements will be provided as additional Lyme disease vaccines are licensed.

Mechanism of action

The protection afforded by currently available Lyme vaccines are dependent on the development of a humoral immune response to rOspA[20]. These antibodies are ingested by the tick from the immunized host during feeding and are active against the *Borrelia* spirochetes in the gut of the tick. Expression of OspA is rapidly downregulated by the Lyme bacterium in response to the blood meal[21]. As a result, the protection conferred by the vaccine depends wholly upon the delivery of high titres of pre-formed antibodies to the gut of an infected tick during feeding.

Antigenic differences in OspA occur between and within *B. burgdorferi* genospecies (e.g. *B. burgdorferi* sensu stricto, *B. afzelii*, *B. garinii*) in both North America and Europe. Although a wide range of mutations, frameshifts, and recombination events in OspA and OspB has been documented, the greatest diversity occurs in European strains; North American isolates are more homogeneous[22]. LYMErix™ does not provide reliable protection against European strains.

Efficacy

Randomized, controlled trial (Phase III) of LYMErix™: The efficacy of LYMErix™ was assessed in a randomized clinical trial of 10,936 subjects aged 15 to 70 years of age recruited at 31 sites in New England, the mid-Atlantic, and north-central United States[23]. Efficacy in preventing "definite" Lyme disease (erythema migrans or objective neurologic, musculoskeletal, or cardiovascular manifestations of Lyme disease, plus laboratory confirmation of infection by cultural isolation, polymerase chain reaction positivity, or Western blot [WB] IgG seroconversion) in the vaccinated cohort after two doses was 49% (95% CI = 15% to 69%) and after three doses was 76% (95% CI = 58% to 86%). (Vaccine efficacy reported in the LYMErix™ product label differs slightly from efficacy reported in the published results of the clinical trial[14] due to reclassification of cases during FDA review. The product label reports an efficacy in preventing definite Lyme disease of 50% after two doses and 78% after three doses). Efficacy in protecting against asymptomatic infection (no recognized symptoms, but with WB IgG seroconversions recorded in year 1 or year 2) was 83% (95% CI = 32% to 97%) in year 1 and 100% (95% CI = 26% to 100%) in year 2.

Care providers and laboratory directors should be advised that vaccine induced anti-rOspA antibodies routinely cause false positive enzyme immunoassay results for Lyme disease[24] and alter the appearance of

immunoblots. However, Western immunoblotting can still be used to discriminate between *B. burgdorferi* infection and previous rOspA immunization, since most patients do not develop anti-OspA antibodies following natural infection, and OspA antibodies are not part of the criteria for a positive diagnosis of *B. burgdorferi* when the recommended procedures are followed[25]. The presence of anti-OspA antibodies does not interfere with the development of serologic responses to other *B. burgdorferi* antigens in individuals who suffer Lyme disease despite vaccination[26].

In southwestern Canada, the presence of *B. hermisii* (the etiologic agent of tick-borne relapsing fever) in ticks can add further complexity to the diagonsis of Lyme borreliosis[27]. The variable clinical presentation of Lyme disease[8] and the complexities of laboratory testing can make the diagnosis of Lyme borreliosis challenging even in areas of high transmission. In regions of little or no risk, which includes virtually all of Canada, this challenge can be particularly daunting and referral to a specialized clinic may be warranted[28].

Safety

In the phase III trial, 5,469 subjects received 30 μg doses of rOspA vaccine with adjuvant, and 5,467 subjects received injections of placebo at enrollment and at 1 and 12 months later[23]. Information on adverse events that were felt to be related or possibly related to injection were available from 4,999 subjects in each group. Soreness at the injection site was the most frequently reported adverse event (24.1% of vaccine recipients vs. 7.6% of placebo recipients, $p < 0.001$). Redness and swelling at the injection site were reported by < 2% of both groups but were significantly more frequent among vaccine recipients than among those who received placebo. Myalgia, influenza-like illness, fever, and chills were significantly more common among vaccine recipients than placebo recipients, but none of these effects was reported by > 3.2% of subjects. Reports of arthritis were not significantly different between vaccine and placebo recipients, but vaccine recipients reported significantly more transient arthralgia and myalgia following each dose of vaccine (SmithKline Beecham, LYMErix™ product monograph). There were no statistically significant differences between vaccine and placebo groups in the incidence of serious or late adverse events, and there were no episodes of immediate hypersensitivity among vaccine recipients[23].

In this same Phase III trial[23], vaccine recipients with a self-reported history of prior Lyme disease had a higher rate of musculoskeletal complaints within 30 days of receiving the vaccine compared to vaccinees without a previous history of Lyme disease (SmithKline Beecham, LYMErix™ product monograph). This difference was not seen among placebo recipients. There was no significant difference between vaccine and placebo groups in the rate of musculoskeletal complaints > 30 days after administration (SmithKline Beecham, LYMErix™ product monograph).

Roughly 10% of adults and 5% of children with Lyme arthritis develop chronic imflammatory joint disease that does not respond to therapy directed against *B. burgdorferi*[29,30]. These individuals are more likely to express certain HLA-DR4 alleles and have high levels of antibody directed against OspA in serum and synovial fluid[31]. It has been proposed that an autoimmune reaction may develop within the joints of these individuals as a result of molecular mimicry between the dominant T cell epitope of OspA and human leukocyte function associated antigen 1 (hLFA-1)[32]. Most recently, severe destructive arthritis has been reported in hamsters vaccinated with outer surface protein A and subsequently challenged with *B. burgdorferi*[33]. The Phase III trial did not detect differences in the incidence of neurologic or rheumatologic disorders between vaccine recipients and their placebo controls in a 2-year post-treatment observation period[23]. However, because of the association between immune reactivity to OspA and treatment resistant Lyme arthritis, the vaccine should not be administered to individuals with a history of treatment resistant Lyme arthritis (SmithKline Beecham, LYMErix™ product monograph).

Persistence of immune response to immunization

Although the correlates of immunity against Lyme Disease are unknown, the currently available Lyme vaccine was not designed to mimic a 'normal' immune response. Rather, antibodies are generated against a tick-phase antigen and act to protect against infection only in the gut of the tick[20]. This unique mechanism of action

strongly suggests that high levels of pre-formed antibodies must be present at the time of an infected bite to confer protection.

A subset of adult subjects enrolled in the Phase III clinical trial of LYMErix™ were studied for the development and durability of rOspA antibodies at months 2, 12, 13, and 20[23]. At month 2, 1 month following the second injection, the geometric mean antibody titre (GMT) was 1,227 enzyme-linked immunosorbent assay (ELISA) units/mL. Ten months later, the GMT had declined to 116 ELISA units/mL. At month 13, 1 month after the third injection, a marked anamnestic response resulted in a GMT of 6,006 ELISA units/mL. At month 20, the mean response had fallen to 1,991 ELISA units/mL (SmithKline Beecham, LYMErix™ product monograph). A limited analysis of antibody titres and the risk of developing Lyme disease suggests that titres >1,200 ELISA units/mL are correlated with protection[23].

RECOMMENDATIONS FOR THE USE OF LYME DISEASE VACCINE

Note 1

Lyme disease vaccine does not protect all recipients against infection with *B. burgdorferi* and offers no protection against Lyme disease acquired outside of North America[22] or other tick-borne diseases (e.g. babesiosis, erlichioses, rickettsioses)[7,27,34]. The vaccine should be considered an adjunct or supplement to personal protective measures against ticks and early diagnosis and treatment of suspected tick-borne infections. Decisions regarding the use of vaccine should be based on individual assessment of the risk of exposure to infected ticks, and on careful consideration of the relative risks and benefits of vaccination compared to other protective measures.

Note 2

Risk assessment in the United States is determined on a county-by-county basis. Risk classification (high, moderate, low, minimal/absent) is based upon detailed epidemiologic information including the presence of the tick vectors (*I. scapularis, I. pacificus*), the predicted prevalence of infection in these ticks, **and** the incidence of clinically recognizable disease[2,3]. Although vector-competent tick populations are present in many regions of southern Canada and adult tick infection rates of up to 10% have been documented (L. Trudel, *Laboratoire de santé publique du Québec*, Ste-Anne de Bellevue, Dr. H. Artsob, Zoonotic Diseases Section, Bureau of Microbiology, LCDC, Winnipeg: personal communications, 2000), there are no regions of Canada that would be classified as 'high' risk and very few areas that would even approach 'moderate' risk.

Persons at high risk

Persons at high risk for *B. burgdorferi* infection are those who reside in or visit areas of high or moderate risk and engage in activities (e.g. recreation, property maintenance, occupational, leisure) that result in **frequent or prolonged** exposure to tick infested habitat. Lyme disease vaccine should only be considered for persons >15 years of age since the product is not currently licensed for younger children.

Persons at moderate risk

Persons at moderate risk for *B. burgdorferi* infection are those who reside in or visit areas of high or moderate risk, **and** are exposed to tick infested habitat, but whose **exposure is neither frequent nor prolonged.** For persons at moderate risk for *B. burgdorferi* infection, Lyme disease vaccine may be considered, but the benefit of vaccination beyond that provided by basic personal protection and early diagnosis and treatment of infection is uncertain.

Persons at low or no risk

Persons at low or no risk for *B. burgdorferi* infection are those who reside in areas of low or no risk as well as those who reside in or visit areas of high or moderate risk **but** have minimal or no exposure to Lyme disease

vector ticks (*I. scapularis*, *I. pacificus*). Lyme disease vaccine is not recommended for persons who are at low or no risk for *B. burgdorferi* infection. The vast majority of Canadians are considered to be at low or no risk of acquiring Lyme disease.

Vaccine schedule

In the Phase III trial, vaccine was administered in single doses of 30 μg at 0-, 1-, and 12-month intervals[23]. Administration was timed to provide maximum protection in advance of the peak tick transmission season, which in endemic areas occurs in the spring and early summer. The vaccine should be administered according to this schedule, so that the second and third doses of vaccine are given several weeks before the beginning of the *B. burgdorferi* transmission season in 2 successive years. More recent evidence suggests that an accelerated schedule of 0, 1, and 6 months also gives excellent antibody titres[35].

Boosters

Whether protective immunity will last > 1 year beyond the 12-month dose is unknown. Published data on the levels of antibody to the protective epitope of OspA during a 20-month period after the first injection of LYMErix™ suggest that boosters may be necessary to maintain long-term immunity[23,36]. In addition, protection against infection is not based on anamnestic recall in the human host, but on the activity of the antibody in the tick gut against *Borellia* during the blood meal[20]. At the current time, there are no data to support the efficacy or safety of booster vaccination with rOspA antigen.

Simultaneous administration with other vaccines

Safety and efficacy of the simultaneous administration of rOspA vaccine with other vaccines has not been established. If LYMErix™ must be given concurrently with other vaccines, each vaccine should be administered in a separate syringe at a separate injection site.

OTHER CONSIDERATIONS

Antibiotic prophylaxis for tick bites

The routine administration of prophylactic antibiotics in the case of a confirmed deer tick bite is not recommended. Even in highly endemic areas (there are no such areas in Canada), the majority (70% to 80%) of deer ticks are not infected with *B. burgdorferi*[37] and the risk of infection after such a bite has been estimated to be approximately 1.4%[38]. Almost all individuals who become infected from a recognized tick bite will develop erythema migrans that is readily recognized and treated. The risk of developing late sequelae from Lyme disease without erythema migrans following a recognized bite is thought to be extremely low[39]. For individuals who remain concerned despite these data, paired early and late (e.g. 6 to 8 weeks) sera can be used to confirm the absence of seroconversion.

Vaccine use in pregnancy or nursing mothers

There is no evidence that pregnancy increases the risk of Lyme disease or its severity. Acute Lyme disease in pregnancy responds well to antibiotic therapy, and adverse fetal outcomes have not been reported in pregnant women receiving standard courses of treatment[8]. Since safety of rOspA vaccines administered during pregnancy has not been established, vaccination of women who are known to be pregnant is not recommended. In addition, unless, substantial risk of infection exists, immunization should be delayed for nursing mothers.

Persons with immunodeficiency

Persons with immunodeficiency were excluded from the single large Phase III safety and efficacy trial[23], and there are no data on Lyme disease vaccine use in this group.

Persons with previous history of Lyme disease

Although persons with a previous history of Lyme disease may have a higher incidence of musculoskeletal complaints in the first month following vaccination than those without such a history, their risk of late musculoskeletal and other adverse events from the vaccine does not appear to be elevated. Vaccination should be considered for persons with a history of previous uncomplicated Lyme arthritis who are at continued high risk[3]. Individuals with a history of treatment resistant Lyme disease should not be vaccinated because of the association between this condition and abnormal immune reactivity to OspA[29-32].

Children

At this time immunization against *B. burgdorferi* is not recommended for children < 15 years old.

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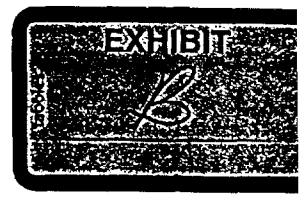


New Vaccinations

Lyme Disease, Rotavirus, Hepatitis A and Pneumococcal Disease

Executive Summary

The purpose of this report is to review the use of the new vaccines for lyme disease, hepatitis A, rotavirus, and pneumococcal disease and to inform primary care physicians of the need for vigilant participation in the Centers for Disease Control and Prevention's (CDC) Vaccine Adverse Event Reporting System (VAERS).

This report presents the clinical use of the new vaccines for Lyme disease, rotavirus, hepatitis A and pneumococcal disease. The Lyme disease vaccine is not universally indicated. Instead, its use should be dependent upon individual risk factors, including both geographical and behavioral factors. While the short-term safety of LYMErix has been determined to be adequate, further clinical research on long term sequelae and disease-related events is necessary.[1] Each year in the United States, the rotavirus infection accounts for an estimated 500,000 physician visits, 50,000 hospitalizations and 20-40 deaths.[2] The rotavirus vaccination (RotaShield®), was initially universally indicated by the CDC's Advisory Committee on Immunization Practices (ACIP). On October 22, 1999, the ACIP, after a review of scientific data, no longer recommends vaccination of infants in the United States and withdraws its recommendation that the RotaShield® vaccine be administered at 2, 4, and 6 months of age.[2,3,60] The hepatitis A vaccine is recommended by the ACIP for anyone more than two years of age desiring immunity and anyone in a high-risk group (high-risk groups include travelers, men who have sex with men, illegal drug users, children living in communities with high incidences, and persons with an occupational risk).[4] On February 17, 1999, the ACIP voted to recommend that universal immunization of children be undertaken in states with an incidence of 20/100,000 or higher.[5,6] Minnesota is not one of the eleven states with an incidence of 20/100,000 or greater. The pneumococcal disease vaccine is universally indicated for individuals over 65 years of age, and is recommended for those between the ages of 2 to 64 if they are immunocompromised, have a chronic illness, and/or live in a special environment such as a nursing home. The burden of pneumococcal disease is enormous in the United States, resulting in an estimated 40,000 deaths, 225,000 cases of pneumonia, 52,000 cases of blood infection and 3,000 cases of meningitis per year.[7] This vaccine is of particular importance in the current context of emerging drug-resistant strains of bacteria.

Feed-back from the VAERS system as well as continued emphasis on research into vaccine efficacy and safety are critical components to realizing the complete benefits of vaccination. Although vaccinations have been dubbed this century's greatest public health achievement, they are continually evolving into more safe and effective forms. For this reason, vigilance on the part of primary care physicians is and will remain a critical component of the efficacy and safety of vaccines.

While the benefits of vaccination to society and the individual often outweigh any associated risks,

continued clinical surveillance as well as ongoing research and development are essential to the minimization of existing risk.

Recommendations

The Lyme disease vaccine should not be administered universally. It is indicated only for those individuals ages 15-70 living in high-risk geographic areas and engaging in high-risk behaviors.

The rotavirus vaccine has been suspended until further studies can rule out a link to intussusception.

The hepatitis A vaccine should be administered universally in high-incidence geographic locations and to any individual in a high-risk category seeking protection.

The pneumococcal disease vaccine should be administered in certain high-risk groups to minimize illness and the emergence of resistant bacterial strains.

Continued research and development are critical to the identification and minimization of existing risk associated with vaccines.

The participation of primary care physicians in VAERS is needed if it is to be a more effective tool for determining vaccine safety and efficacy.

Introduction

Vaccinations have been dubbed this century's greatest public health achievement, and their routine implementation has resulted in significantly decreased morbidity and mortality in infants worldwide.[8] Although seen by many as a magic bullet, vaccinations are very seldom perfect when initially released by manufacturers, and go through significant growing pains as they evolve. It is critical that physicians, researchers and the public support crucial continued research and development on existing as well as new vaccinations.

History reveals a multitude of common and well-known immunizations that have gone through significant evolution in order to achieve their current levels of efficacy and safety. The first measles vaccines were licensed for use in the U.S. in 1963, and at that time one inactivated and one live attenuated vaccine (Edmonston B strain) were introduced. The inactivated vaccine was not immunogenic and sometimes resulted in infection with atypical measles. The Edmonston B vaccine was withdrawn in 1975 as there was an increased incidence of fever and rash associated with it. Two live, further attenuated vaccines, the Schwarz strain and the Moraten strain, were introduced and subsequently replaced by a fourth vaccine, the currently used Enders-Edmonston vaccine. Each successive strain resulted in fewer adverse events.

In 1969, three vaccines against rubella were licensed for use in the United States: HPV-77:DE-5 (from duck embryo), HPV-77:DK-12 (from dog kidney), and Cendehill strains (from rabbit kidney). HPV-77:DK-12 was withdrawn from the market due to a high rate of associated joint problems. In 1979, all strains were discontinued with the introduction of RA 27/3 (from human diploid fibroblast) which is still currently used. The whole-cell pertussis vaccine was used from its introduction in the 1930's until 1991 unchanged. Concerns about adverse systemic reactions such as convulsions, acute encephalopathy, and lasting brain damage led scientists to develop the acellular pertussis vaccine, which was licensed for use in 1991. Adverse events such as convulsions, persistent crying, and hypotonic hyporesponsive episodes occurred at a higher rate among infants vaccinated with the whole cell vaccine than with the acellular vaccine.

The inactivated poliovirus vaccine (IPV), which is injectable, was first licensed in 1955. With the advent of the live oral poliovirus vaccine (OPV) in 1961, IPV was essentially replaced due to factors such as ease of administration, cost and efficacy. However, with global polio eradication goals almost met and elimination of wild type poliovirus in the Western hemisphere, the risk of paralytic polio associated with OPV is considered unacceptable (the risk is 1 in 52,400,000). In January of 1997, the Advisory Committee on Immunization Practices changed their recommendations for polio to advise that routine childhood immunization consist of two doses of IPV followed by two of OPV.[9] In 1999, the universal childhood immunization schedule was changed by ACIP to reflect these recommendations.[10] On June 17, 1999, the ACIP voted to use IPV for all four doses in childhood immunization.[11] This vote became a final recommendation when it was published in the CDC's October 1, 1999 issue of the Morbidity and Mortality Weekly Report.[56]

The ACIP's recommendation for universal vaccination of infants against hepatitis B has resulted in a closer assessment of thimerosal-containing vaccinations.[10] Concerns over thimerosal, a mercury-containing compound, have recently encouraged the American Academy of Pediatrics (AAP) to release a new set of recommended indications for the hepatitis B vaccine. In July of 1999, the AAP stated that a new thimerosal-free hepatitis B vaccine should be the goal, but until then, vaccination of all infants of mothers who screen negative for HbsAg should be postponed until two to six months of age. Premature infants should not be vaccinated until they are at least 2.5 kilograms and infants of mothers who screen positive for HbsAg should be immunized according to standing ACIP recommendations. In populations where routine screening of pregnant women for hepatitis B antigens is not implemented, all infants should be vaccinated according to current ACIP recommendations.[12,13] With the advent of a thimerosal-free Hepatitis B vaccine in September of 1999, the recommendations reverted to their original form.[57]

On July 15, 1999, the CDC recommended that use of the newly licensed rotavirus vaccine be suspended until at least November of 1999 due to reports of possible increases in intussusception rates in vaccinated infants.[3] This suspension was prompted largely by information gathered by the CDC's vaccine adverse event reporting system (VAERS) and demonstrates how accurate and timely reporting can contribute to the increased safety of vaccinations. On October 16, 1999, the manufacturer of Rotashield withdrew the vaccine from the market until further studies can confirm or deny links between intussusception and the vaccine.[58] The rotavirus vaccine had been recommended for universal use in infants by the ACIP in March of 1999.[2]

Lyme Disease Vaccine

On December 21, 1998, the Food and Drug Administration approved LYMErix$_{TM}$, Smith-Kline Beecham's new vaccine against Lyme disease. The availability of this vaccine has engendered the need for guidelines on its appropriate role in the prevention of Lyme disease. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recently met this challenge when it issued its report "Recommendations for the Use of Lyme Disease Vaccine Recommendations of the Advisory Committee on Immunization Practices". In its statement, the ACIP recommends that decisions regarding vaccine use be based on individual risk factors, both geographic and behavioral.[1] The American Medical Association (AMA) and the American Academy of Pediatrics (AAP) have not released official policy statements regarding the recommended use of this vaccine. This may be due to the fact that universal vaccination is not being advocated and the vaccine is only authorized for use in individuals aged 15 to 70 years. The AMA has, however, endorsed the view that the vaccine should not be used universally, but instead should be targeted to groups of individuals with specific characteristics

based on area of residence and participation in high-risk activities.[14] The American Academy of Family Physicians (AAFP) recently released a new policy outlining recommendations for the use of the Lyme disease vaccine which closely resemble the recommendations of the ACIP and the position of AMA.[15] There is general consensus within the medical and public health communities that the use of LYMErix should be targeted to specific groups and this is reflected in all of the referenced literature.

Lyme disease is the most common vector-borne disease in the United States. It is caused by the spirochete (a spiral bacterium of the order Spirochaetales) *Borrelia burgdorferi* and is transmitted by the bite of an infected deer tick *(Ixodes scapularis)* or Western black-legged tick *(Ixodes pacificus).* The spirochete is not usually transmitted to the host until the tick has been attached for about 36-48 hours and so the successful transmission of the spirochete can be minimized through daily personal examinations for ticks.[16] Symptoms of Lyme Disease may include a bulls-eye shaped rash around the infected bite (erythema migrans), a fever, malaise, stiff neck, headache, fatigue, myalgia, and arthralgia. Manifestations of early-disseminated infection include cardiac, neurologic, and musculoskeletal disease. Late-disseminated disease manifestations include personality changes, sleep disruptions, cognitive disorders (if encephalopathy is present), swelling and pain of joints, and axonal polyneuropathy (pathology of the nervous system, specifically of the axons). If the disease is caught early in its progression (less than three weeks), it is almost always amenable to treatment with antibiotics, most often amoxicillin and doxycycline.[1,17] Personal prevention measures are critical in the control of Lyme disease, such as wearing light-colored clothing with long sleeves and pant legs, tucking pants into socks, checking twice a day for ticks, and using insect repellant with DEET.[1]

Lyme disease is endemic to the Northeast, Upper Midwest (*Ixodes scapularis*) and the West Coast (*Ixodes pacificus*), with these areas together accounting for approximately ninety percent of all reported cases of Lyme Disease in the United States.[14] The CDC has stated that during 1993-1997, a mean of 12,541 cases annually of Lyme disease were reported in the United States, and in 1998, the incidence was 6.06 (per 100,000 people).[1,18] The Minnesota Department of Health documented a total of 261 confirmed cases of Lyme disease in 1998. This translates to an approximate incidence of 5.6/100,000. In Minnesota the cases of Lyme disease are not uniformly distributed throughout the state, so the incidence will vary in different places within the state (Appendix I).[19] In 1998, the state of Connecticut reported an incidence of 90.77/100,000, the highest in the United States. New York, New Jersey, Pennsylvania, Massachusetts, Maryland, Rhode Island, and Wisconsin all had reported 1998 incidences of greater than 10/100,000, or a rate of infection of .0001 or greater.[18]

The Lyme disease vaccine is made from a recombinant *Borrelia burgdorferi* surface lipoprotein with known human immunogenicity, rOspA, as expressed by transformed E. coli cells. This protein is antigenic and causes a humoral immune response in humans, resulting in the production of anti-OspA antibodies. OspA is expressed primarily by *Borrelia burgdorferi* while it is in the gut of the tick, at initiation of feeding. However, upon passing by the tick salivary gland into the host bloodstream, *Borrelia burgdorferi* predominantly expresses another outer surface lipoprotein, OspC. Therefore, anti-OspA antibody will have its primary effect upon the causative agent in the gut of the tick, as the host blood is ingested, resulting in the destruction of *Borrelia burgdorferi* prior to its entry into the host bloodstream. Therefore, once the *Borrelia burgdorferi* has entered the host and is thus expressing primarily OspC, the LYMErix vaccine is largely ineffective.[1]

Patient Selection

The LYMErix vaccine is not universally indicated. It is for use in individuals aged 15 to 70 years, those living in or traveling to high incidence areas, and those exhibiting high-risk behaviors (hiking, gardening,

landscaping). It is not recommended for use in pregnant women, breast-feeding women, immunodeficient individuals, persons with musculoskeletal disease or with treatment-resistant Lyme arthritis.[20] The vaccine is administered in three doses at zero, one and twelve months, with protective boosters potentially needed on an undetermined basis.

Effectiveness

The major efficacy trial conducted by The Lyme Disease Vaccine Study Group enrolled 10, 936 people at 31 sites in 10 different states with very high incidences of Lyme disease. Of these, 5469 were administered vaccine, while 5467 were administered placebo. The vaccine consisted of 30 μg of lipidized rOspA adsorbed to an aluminum hydroxide adjuvant in phosphate-buffered saline. The placebo was identical except did not contain the lipidized rOspA. The vaccine was determined to be 49% effective after the first two dosages, and 76% effective after all three in definite cases of Lyme disease.[21] In asymptomatic Lyme disease, as determined by Western blot seroconversions, the efficacy jumps to 83% after the first two dosages, and up to 100% after the full course of injections.[1] The LYMErix vaccine is associated with local reactions including soreness (24.1%), swelling and redness (less than 2%), and systemic reactions including fever, chills, and myalgia (less than 3.2%). The occurrence of late events or clinical syndromes in the vaccine group was not statistically significantly higher than in the placebo group.[21]

While the short term safety of LYMErix was determined to be adequate in the efficacy trial, further research on long term chronic sequelae and disease-related events is necessary. One particular concern over the long term safety of the Lyme disease vaccine is the possibility that it may trigger arthritis or paresthesias in genetically prone individuals. Individuals who exhibit the HLA type DR4 genotype (the human leukocyte antigen type DR4) are predisposed to rheumatoid arthritis, which is considered to be an autoimmune disease. Individuals with this genotype are also predisposed to treatment-resistant Lyme arthritis, possibly because the protein hLFA-1 (human leukocyte function associated antigen), which has a high binding affinity to HLA-DR4, has a high homology with OspA. This may result in the anti-rOspA antibodies acting as autoantibodies against the hLFA-1 protein when it is presented by HLA-DR4.[14,22] There are general concerns that this vaccine may result in a "late unanticipated event" and that vaccinees should be followed carefully for at least 5-10 years after vaccination to obtain appropriate data on long term effects.[23] The issue of booster shots after initial vaccination to maintain anti-OSA antibody titers needs to be researched. Since children under the age of fifteen comprise a large portion of those individuals at-risk, the vaccine needs to be modified so it is indicated for children under fifteen. Finally, this vaccination will result in routine false-positives when testing is done with the traditional ELISA method, and the CDC suggests using Western blotting instead when testing a vaccinated individual for Lyme disease.[1]

Cost

Universal administration of LYMErix is not cost-effective at currently reported statewide incidences. Meltzer et al. report that with a total vaccine cost of $200, vaccine efficacy of .85, probability of early diagnosis and treatment of .80, and probability of Lyme disease infection of .005 (500/100,000), the cost per case of Lyme disease averted is $39,761.[24] Currently, a single vaccine dose costs $49, which in addition to administration costs, amounts to a total vaccine cost of approximately $200 for the three shot series. The highest reported incidence of Lyme disease in 1998 was in Connecticut, at 90/100,000, or .0009. The vaccine efficacy, according to the literature, ranges from 78% in cases of symptomatic Lyme disease to 100% in cases of asymptomatic Lyme disease (.78 - 1.0). The estimate of .80 for the early diagnosis of Lyme disease may result in the understatement of disease related costs, as the range

suggested in the literature for early diagnosis varies from .60 - .90. A recent report by the Institute of Medicine describes a system for ranking the relative cost-effectiveness of pursuing either research and development of candidate vaccines or of implementing vaccine programs.[25] This report ranks those vaccines costing in excess of $100,000/QALY (quality-adjusted life year) saved as less favorable. The universal administration of the Lyme disease vaccine falls into this category.

Rotavirus Vaccine

The tetravalent, oral, live rotavirus vaccine, RotaShield® (Wyeth-Ayherst), was approved for use in infants by the FDA on August 31, 1998. Rotavirus is a 70-nanometer-diameter icosahedral virus composed of three capsid protein layers and 11 double-stranded RNA segments.[31] It contains three major antigenic proteins, one of which, viral protein 7 (VP7) a G-type surface protein, is specifically used in the tetravalent RotaShield vaccine. Using gene reassortment, the VP7 gene from three of the four human serotypes was incorporated into the rhesus rotavirus, making three single-gene human-rhesus reassortants. The VP7 gene present in the native rhesus rotavirus strain provides immunity to the fourth human serotype.[27] Using a combination of the native rhesus rotavirus and the three reassortant strains, the tetravalent RotaShield will protect against all four significant human rotavirus serotypes.

On July 15, 1999, the CDC recommended that use of the newly licensed rotavirus vaccine be suspended until at least November of 1999, due to reports of possible increases in intussusception rates in vaccinated infants.[3] Prior to that, the rotavirus vaccine had been recommended for universal use in infants by the ACIP in March of 1999.[2] However, on October 22, 1999, the ACIP, after a review of scientific data which indicated a strong association between RotaShield and intussusception among some infants during the first 1-2 weeks following vaccination, withdrew its recommendation of the RotaShield® vaccine.

Patient Selection

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) originally released its recommendation for universal vaccination of infants on March 19, 1999. The vaccination was recommended to be administered at 2, 4 and 6 months of age, but not after 7 months of age due to declines in maternal antibodies and subsequent increases in febrile illness associated with the vaccination. The entire three-dose course was to be completed within the first year of life, as data regarding both efficacy and safety in children aged one or older was not adequate. If the vaccination series was initiated late, then each dose was to be at least three weeks apart.[2] Prior to their withdrawal of the vaccine, the ACIP revised its recommendations to encourage immunization of premature infants if they met the following three requirements: greater than six weeks of age, leaving the nursery or no longer hospitalized, and clinically stable. At that time, the ACIP suggested that although there may be more risks for premature infants from the vaccine, the rotavirus infection itself also poses a large threat, and so costs and benefits of both options must be weighed properly.[26] The vaccine was recommended for breast-fed infants and those who have had rotavirus gastroenteritis previously, and for those who had a mild illness with no fever. RotaShield could be safely administered simultaneously with DTP (or DTaP), Hib vaccine, OPV, IPV, and hepatitis B.[27] RotaShield was not be given to immunocompromised infants, infants with acute to moderate gastrointestinal disease, moderate to severe febrile illness, preexisting chronic gastrointestinal disease or infants allergic to any part of the vaccine. If an infant regurgitated a dose of the vaccine, it was not be re-administered, as data on the safety of higher doses was not sufficient. The American Academy of Pediatrics (AAP) had also released a recommendation for universal rotavirus vaccination at ages 2, 4 and 6 months. The recommendations of the ACIP and the AAP were very similar, except the AAP suggested not to initiate the course of

vaccinations after six months of age, while the ACIP suggested seven months of age.[28] The American Academy of Family Physicians (AAFP), however, did not support universal vaccination, and released a set of recommendations which stated that rotavirus vaccination should be an individual decision made collaboratively by the parents and physician.[29] The rotavirus vaccination was added to the Recommended Childhood Immunization Schedule for 1999 prior to the recall of the rotavirus vaccine.[30]

Effectiveness

The rotavirus vaccine was determined to be both safe and acceptably effective in several clinical trials. However, based on the results of an expedited review of scientific data presented to the ACIP by CDC in cooperation with the FDA, NIH, and Public Health officials, along with Wyeth-Lederle indicated a strong association between RotaShield and intussusception leading to its withdrawal on October 22, 1999.[60] Originally, it was thought that the adverse events found to be associated with vaccine administration to more than 10,000 children included a mild fever in up to 15% of recipients, a moderate fever in about 1% of recipients, loss of appetite, fussiness and fatigue.[32] The febrile response usually occurred on the third or fourth day following vaccine administration. There was thought to be no statistically significant difference in occurrence of diarrhea, intussusception, vomiting, coughing or rhinitis in placebo-controlled clinical safety trials. However, one efficacy study in Finland found a higher rate of diarrhea in vaccinated children than in placebo recipients.[2,33] Four efficacy trials for RotaShield in the United States and Finland determined that the vaccine demonstrates 49%-68% efficacy against any rotavirus infection, 69%-91% against severe diarrhea, and 50%-100% efficacy in prevention of visits to the physician's office.[2] In one trial in Finland, the efficacy of the vaccine in preventing hospitalizations was examined, and the protection was determined to be 100%.[33] As was expected by vaccine-developers, RotaShield protected most effectively against severe disease, enhancing its overall cost-effectiveness.

Cost

Rotavirus is the most common cause of severe childhood gastroenteritis and exhibits symptoms including diarrhea, fever, abdominal cramping, and vomiting and often results in severe dehydration. Four out of five children are infected before the age of five, resulting in approximately 3.5 million infected children in the United States per year. This results in 500,000 physician visits, 50,000 hospitalizations and 20-40 deaths a year in the U.S.[2] Worldwide, as many as 870,000 children die from rotavirus infection per year.[34] A study by Tucker et al. demonstrates the cost-effectiveness of the RotaShield vaccine when administered routinely and universally to infants. Direct medical costs are estimated at $264 million, and societal costs at $1 billion, which upon threshold analysis yields a break-even cost of vaccine of $9 a dose for the health care system and $51 a dose for society.[35] With current prices ranging from $20 a dose to $38 a dose, universal vaccination against rotavirus is always cost-effective for society.[32,36] The cost of vaccine, vaccine efficacy, and disease burden all affect the cost-effectiveness of a universal vaccination program. According to a forthcoming report by the Institute of Medicine, the rotavirus vaccine falls into the favorable category, as it incurs a cost of between $10,000 and $100,000 per QALY (quality-adjusted life year) saved.[25]

The development of a vaccine against rotavirus is extremely important considering that there is apparently no reliable prevention method for controlling its spread. The rates of infection are the same among children in developing and developed countries, so hygiene measures and clean water have had little effect on the rates of transmission of rotavirus.[2] In a clinical efficacy study in Caracas, Venezuela, it was found that members in both the placebo group and vaccine group shed a vaccine virus, indicating that there is transmission of this virus in the community.[37] This indicates that vaccinated individuals may

confer resistance to rotavirus to non-vaccinated individuals.

Hepatitis A Vaccine

Two hepatitis A vaccines, HAVRIX® (SmithKline Beecham) and VAQTA® (Merck), are available for use in the United States. Hepatitis A, caused by a 27-nm non-enveloped RNA picornavirus (enterovirus) with only one serotype, is native to humans but can be harbored in primates. Both HAVRIX and VAQTA are composed of whole, formalin-inactivated hepatitis A virus particles adsorbed onto aluminum hydroxide, administered in a two-shot series given at least six months apart. While HAVRIX is currently licensed in three formulations with varying E.L.U.'s (ELISA units), VAQTA is licensed in two formulations, with varying U's (units of antigen). Neither is indicated for children less than two years of age, individuals with moderate to severe illness, individuals who are allergic to any component of the vaccine, and, as only limited data for pregnant women is available, pregnant women.

Patient Selection

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) published a set of recommendations for use of the hepatitis A vaccine, which state that it should be used for anyone over the age of two who desires immunity, and persons in a high-risk group. High risk groups include travelers, children living in communities with high rates of infection, men who have sex with men, illegal drug users, persons with an occupational risk for infection (research laboratory setting or those working with primates), persons with chronic liver disease, and persons with clotting-factor disorders.[4] Safety, immunogenicity and efficacy studies are currently underway for Avaxim, a new childhood vaccine for hepatitis A which could be used in children as young as 18 months.[38] The recommended use guidelines published by The American Academy of Pediatrics (AAP) are very similar to those of the ACIP, also suggesting that vaccine use be restricted to individuals older than two years of age and in high-risk groups.[39] Both guidelines recommend passive immunization with gamma globulin for postexposure prophylaxis, as there is limited data available regarding the efficacy of the vaccine in this situation. Both the American Medical Association (AMA) and the AAP concur with these recommendations, noting that the highest rates of infection are usually found in children aged 5 to 14 years of age, and therefore that immunization of children and adolescents is particularly germane when considering incidence reduction.[40,41]

On February 17, 1999, the ACIP voted to recommend that universal immunization of children be undertaken in states with an incidence of 20/100,000 (.0002) or higher.[6] This includes eleven states: Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Nevada, California, and Idaho. Oklahoma has instituted state school entrance requirements that include hepatitis A immunization for children entering kindergarten and seventh grade.[42,43] In Maricopa county in Arizona, vaccination is required for children ages 2 to 5 for day care entry, and both Texas (select counties) and Alaska are implementing routine vaccination programs, although there are no concurrent school entry requirements.[44] For states with an incidence ranging between 10/100,000 and 20/100,000, routine immunization should be considered, according to the ACIP. The current average national incidence in the U.S. is 10/100,000. Other states are expected to institute routine hepatitis A vaccination for children in response to the new ACIP recommendations, although funding is a consideration.[42]

Effectiveness

The efficacy of the HAVRIX vaccine, evaluated in a double-blind placebo-controlled randomized study

on 40,000 children ages 1 to 16 in Thailand, was determined to be 94%. For VAQTA, the efficacy rate was found to be 100% as determined by a study of 1000 children in New York. Although hepatitis A does not result in chronic disease, it is a cause of serious morbidity and even in some cases, mortality. In the United States, it is estimated that 150,000 cases of hepatitis occur per year, with fulminant hepatitis resulting in approximately 100 deaths per year for a case-fatality rate of approximately 0.3%. Symptoms include dark urine, nausea, vomiting, diarrhea, jaundice, appetite loss and fatigue and there is little treatment for the disease besides rest and proper diet. The route of transmission is oral-fecal, with the majority of transmission occurring in private homes but occasionally occurring via contaminated food or water. The incubation period averages 28 days, with symptoms lasting up to two months. Children under six years of age are usually asymptomatic, and therefore constitute a primary source of transmission.[4] HAVRIX and VAQTA have been administered to over 59,000 people in clinical trials and are associated with mild problems, such as soreness at injection site, headache, loss of appetite, and fatigue. Occurrence of serious adverse reactions in the vaccinated group were not documented at levels above expected background incidence.

Cost

With approximately 150,000 cases of hepatitis A per year in the United States, costs range up to as much as $450 million dollars per year (medical and social costs). A study by Dr. Ananya Das indicates that the strategy of universal vaccination, with outcome measures of cost per person and quality life years gained, is cost-effective, with a marginal cost-effectiveness ratio of $12, 833.[45] According to a report by the Institute of Medicine, with a cost of $12,833 per QALY (quality-adjusted life year) saved, universal vaccination against hepatitis A falls into Level III, the favorable category. The study also determined that a strategy of screening for antibody followed by vaccination when appropriate was cost-effective, with a cost-effectiveness ratio of $7,267.[45] According to the Institute of Medicine study, this strategy would fall into Level II, the more favorable category, with a cost of $7,267 per QALY.[25] Das' study also found that when the cost of the two-dose vaccination fell below $57, the strategy of universal vaccination was favored over the screen and vaccinate strategy. With current costs of about $33 per dose, the screen and vaccinate strategy may be more cost-effective than universal vaccination.[46] A new study on a combined pediatric hepatitis A/ hepatitis B vaccine indicates that it is both safe and efficacious in children ages 1 to 16.[47] This finding will most likely result in significantly reduced associated costs of administration, making implementation of universal vaccination more attractive. The hepatitis B vaccination is already universally indicated and is listed on the recommended child immunization schedule released by the ACIP.

Pneumococcal Disease Vaccine

The two vaccines currently available for pneumococcal disease, Pneumovax 23® (Merck) and Pnu-Immune 23® (Lederle Laboratories) have been available in their present form since 1983, when their licensure allowed for the replacement of an existing 14-valent vaccine. Pneumovax and Pnu-Immune are made of purified capsular polysaccharide antigen from 23 serotypes known to cause invasive disease (isolated from the blood of infected individuals). These 23 serotypes account for 85-90% of all invasive pneumococcal disease. A single dose contains 25 mg of each capsular polysaccharide antigen dissolved in saline solution with either phenol or thimerosal as a preservative.

Patient Selection

With an alarming increase in the incidence of bacterial resistance to antibiotics, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends

extensive use of the vaccine in certain populations in an attempt to deter the emergence of multi-drug resistant strains of Streptococcus pneumoniae bacteria. ACIP recommends that individuals in the following groups receive a pneumococcal disease vaccination: those aged greater than or equal to 65 years of age, those aged 2 to 64 years with a chronic illness or functional or anatomic asplenia, those living in a special environment (nursing home, long-term care facility), and immunocompromised individuals.[7] Revaccination is particularly important, and is suggested for those with unknown immunization status, those older than 65 if more than five years have elapsed since immunization, those sensitive to infection and older than 10 years if more than five years have elapsed, and those sensitive to infection and younger than 10 years if more than three years have elapsed.[48] In March of 1999, the American Medical Association (AMA), in conjunction with ten other professional medical organizations, released a Quality Care Alert stating the critical importance of immunization against Streptococcus pneumoniae in high-risk groups and revaccination efforts.[49] The American Academy of Pediatrics (AAP) states that there are over 340,000 individuals aged 2 to 18 years who have chronic diseases, placing them in the high-risk group for invasive pneumococcal disease. AAP recommends that these individuals receive vaccination, and that those at the highest risk for rapidly decreasing antibody titers (immunocompromised individuals) receive revaccination every three or five years, depending on the age of recipient.[40] Adult immunization is often very difficult to achieve, and it is currently estimated that less than 45% of those over 65 years of age are immunized. This is of particular concern in the context of emerging drug-resistant strains of bacteria.

Effectiveness

The vaccines for pneumococcal disease generally demonstrate high rates of efficacy against invasive disease, ranging from 56%-81% as demonstrated in controlled clinical trials in South Africa, France, and case-controlled studies.[50] The rate among those aged 65 years or greater was 75%, while the rate within specific groups (those with anatomic asplenia, diabetes mellitus, chronic pulmonary disease, congestive heart failure, and coronary heart disease) ranged from 65%-84%. Vaccine efficacy has not been established in immunocompromised individuals and it is thought that these individuals will have a poor antibody response to the antigens in the vaccine (due to age or immunosuppressive treatment). The vaccines are effective only against invasive disease (bacteremia and meningitis) and pneumococcal pneumonia and are not proven to be effective against sinusitis or otitis media. Furthermore, the vaccines are not immunogenic in children aged less than two years. In children of this age the immune system is immature, and the induced antibody response, which is T-cell-independent, is often inconsistent and not adequate enough to provide protection when challenged with Streptococcus pneumoniae. The vaccine is safe, and has been used since 1977. The most common adverse reactions are pain, redness and swelling at the site and erythema. Other reactions, such as anaphylactic, systemic or severe local reactions, are extremely rare. The vaccine is not indicated for those less than two years of age, those with an allergy to any of the vaccine components and pregnant or nursing women.[7] The symptoms of pneumococcal disease include shaking chills, cough, fever, chest congestion, headache and greenish, rusty or yellowish sputum.[51] Treatment is currently not reliable due to increasing bacterial resistance to antibiotics, and therefore vaccination, especially in vulnerable individuals, is critical.

Cost

The burden of pneumococcal disease is enormous in the United States, as well as worldwide. It accounts for approximately 40,000 deaths, 225,000 cases of pneumonia, 52,000 cases of blood infection, and 3,000 cases of meningitis per year in the United States. The incidence of pneumococcal bacteremia is 15-30/100,000 and the incidence of pneumococcal meningitis is 1-2/100,000.[7] Worldwide, more than 1.2 million children die from pneumococcal disease.[52] In a cost-effectiveness study conducted by Sisk et al.

the pneumococcal vaccine was found to be both cost-effective and cost saving. It concluded that if 23 million unvaccinated individuals over the age of 65 had been vaccinated, 78,000 years of healthy life would have been gained, and $194 million would have been saved. The vaccination was considered cost saving in those older than 65 years if the vaccine cost $20 or less, and in the year 1993, Medicare covered the vaccine at $12.[53] With the base case analysis revealing cost savings per quality-adjusted life year (QALY), the Institute of Medicine ranked the vaccine for pneumococcal disease, in the Most Favorable category, as it saves both money and QALY's. The Institute of Medicine suggests that this ranking is dependent upon vaccination of populations greater than 65 and less than two.[25] There is currently a vaccine, PNCRM7, being developed by Wyeth-Lederle which has proven to be safe in clinical trials, and which was shown to be 100% effective in clinical studies. As a result of these promising results, the vaccine has been given fast-track development status by the FDA. The vaccine is a seven-valent vaccine which will protect against invasive pneumococcal disease and otitis media, which cause up to 30 million pediatric visits a year in the United States.[54] The study by Sisk et al. provides strong economic and health reasons for the extensive use of the vaccines for pneumococcal disease.

VAERS

Immunizations represent the intersection of personal health care and public health initiatives. It is critical that research and development efforts continue to be supported by the medical, scientific and public health communities as vaccines are continually evolving as we gain more knowledge about disease processes and immunology. This continuing evolution prompted the CDC to establish the Vaccine Adverse Event Reporting System (VAERS) in November 1990 for use in the ongoing evaluation of the safety and efficacy of vaccines. VAERS is a particularly important tool for determining vaccine safety and its use should be promoted by physicians and manufacturers. VAERS accepts reports of any adverse event following vaccination and compiles the information, allowing the CDC to track any unusual epidemiological trends associated with vaccine safety. Appendix I contains a copy of the VAERS reporting form. For information on how to contact the VAERS program see Appendix II.

Although the data is subject to limitations, VAERS cannot be a totally successful tool without physician reporting. Each report provides information that is compiled to assess vaccine safety. Complete and accurate reporting of post-vaccination events supplies public health professionals with the information they need to ensure the safest strategies of vaccine administration. From January 1991 to December 1996, only 14.5% of the reports received by VAERS were from private health care providers, while 71.8% were from manufacturers and public health departments.[55] Physicians must be willing to foster the VAERS system by making parents aware of the possibility of a post vaccine adverse event and encouraging reporting of such events. VAERS is a tool that allows the scientific and medical community to further reduce risks associated with vaccines. Without personal alertness and advocacy at the individual level on the part of private health care providers, VAERS can not reach it's envisioned potential.

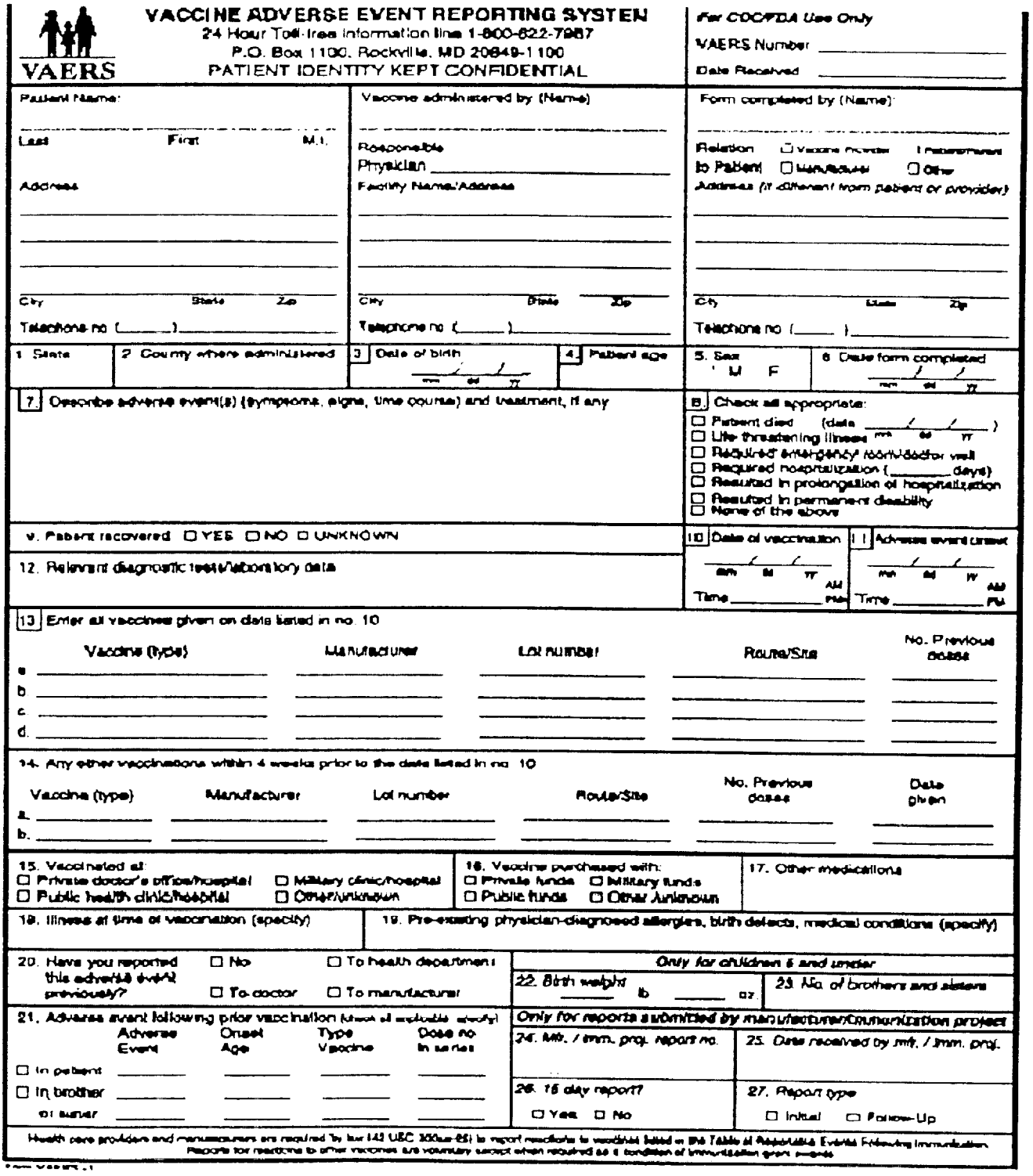
Recommendations

- The Lyme Disease vaccine should not be administered universally. It is indicated only for those individuals ages 15-70 living in high-risk geographic areas and engaging in high-risk behaviors.
- The Rotavirus vaccine has been suspended until further studies can rule out a link to intussusception.
- The Hepatitis A vaccine should be administered universally in high- incidence geographic locations and to any individual in a high-risk category seeking protection.
- The pneumococcal disease vaccine should be administered in certain high-risk groups to minimize

illness and the emergence of resistant bacterial strains.

- Continued research and development are critical to the identification and inimization of existing risk associated with vaccines
- The participation of primary care physicians in VAERS is needed if it is to be a more effective tool for determining vaccine safety and efficacy.

Appendix I: The VAERS Reporting Form[55]



VACCINE ADVERSE EVENT REPORTING SYSTEN
24 Hour Toll-free Information line 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number
Date Received

Patient Name: Last First M.I.
Address
City State Zip
Telephone no. ( )

Vaccine administered by (Name)
Responsible Physician
Facility Name/Address
City State Zip
Telephone no. ( )

Form completed by (Name)
Relation to Patient: Vaccine provider / Parent/guardian / Manufacturer / Other
Address (if different from patient or provider)
City State Zip
Telephone no. ( )

1. State
2. County where administered
3. Date of birth (mm dd yy)
4. Patient age
5. Sex: M F
6. Date form completed (mm dd yy)

7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
- Patient died (date mm dd yy)
- Life threatening illness
- Required emergency room/doctor visit
- Required hospitalization (days)
- Resulted in prolongation of hospitalization
- Resulted in permanent disability
- None of the above

9. Patient recovered: YES NO UNKNOWN

10. Date of vaccination (mm dd yy) Time AM PM

11. Adverse event onset (mm dd yy) Time AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
- Private doctor's office/hospital
- Military clinic/hospital
- Public health clinic/hospital
- Other/unknown

16. Vaccine purchased with:
- Private funds
- Military funds
- Public funds
- Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously?
- No
- To health department
- To doctor
- To manufacturer

Only for children 6 and under
22. Birth weight lb oz
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
In patient				
In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr. / imm. proj. report no.
25. Date received by mfr. / imm. proj.
26. 15 day report? Yes No
27. Report type: Initial Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant projects.

DIRECTIONS FOR COMPLETING FORM

Additional pages may be attached if more space is needed.

GENERAL

Use a separate form for each patient. Complete the form to the best of your abilities. Items 3, 4, 7, 8, 10, 11, and 13 are considered essential and should be completed whenever possible. Parents/Guardians may need to consult the facility where the vaccine was administered for some of the information (such as manufacturer, lot number or laboratory data.)

Refer to the Reportable Events Table (RET) for events mandated for reporting by law. Reporting for other serious events felt to be related but not on the RET is encouraged.

Health care providers other than the vaccine administrator (VA) treating a patient for a suspected adverse event should notify the

VA and provide the Information about the adverse event to allow the VA to complete the form to meet the VA's legal responsibility. These data will be used to increase understanding of adverse events following vaccination and will become part of CDC Privacy

Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems". Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

Postage will be paid by addressee. Forms may be photocopied (must be front & back on same sheet).

SPECIFIC INSTRUCTIONS

Form Completed By: To be used by parents/guardians, vaccine manufacturers/distributors, vaccine administrators, and/or the person completing the form on behalf of the patient or the health professional who administered the vaccine.

Item 7: Describe the suspected adverse event. Such things as temperature, local and general signs and symptoms, time course, duration of symptoms diagnosis, treatment and recovery should be noted.

Item 9: Check "YES' if the patients health condition is the same as it was prior to the vaccine, 'NO' if the patient has not returned to the pre-vaccination state of health, or UNKNOWN" if the patient's condition is not known.

Item 10: Give dates and times as specifically as you can remember. If you do not know the exact time, please

Item 11: indicate "AM" or "PM" when possible if this information is known. If more than one adverse event, give the onset date and time for the most serious event.

Item 12: Include "negative" or "normal" results of any relevant tests performed as well as abnormal findings.

Item 13: List ONLY those vaccines given on the day listed in Item 10.

Item 14: List any other vaccines that the patient received within 4 weeks prior to the date listed in

Item 16: This section refers to how the person who gave the vaccine purchased It, not to the patient's insurance.

Item 17: List any prescription or non-prescription medications the patient was taking when the vaccine(s) was given.

Item 18: List any short term Illnesses the patient had on the date the vaccine(s) was given (i.e., cold, flu, ear Infection).

Item 19: List any pre-existing physician-diagnosed allergies, birth defects, medical conditions (including developmental and/or neurologic disorders) for the patient.

Item 21: List any suspected adverse events the patient, or the patient's brothers or sisters, may have had to previous vaccinations. If more than one brother or sister, or if the patient has reacted to more than one prior vaccine, use additional pages to explain completely. For the onset age of a patient, provide the age in months if less than two years old.

Item 26: This space Is for manufacturers' use only.

Appendix II: VAERS Contact Information[55]

Who can report to VAERS?

Any one can report to VAERS. VAERS reports are usually submitted by health care providers, vaccine manufacturers, and vaccine recipients (or their parents/guardians). Patients, parents, and guardians are encouraged to seek the help of a health care professional in reporting to VAERS.

The Reportable Events Table specifically outlines the post-vaccination events which must be reported. The need to report is also based on the amount of time which elapsed between the vaccination and the start of the event. A copy of the table can be obtained by calling VAERS at 1-800-822-7967.

How do I report to VAERS?

A VAERS report form, pre-addressed to VAERS and postage-paid, is used to report pertinent information, including a narrative description of the adverse event.

For a VAERS report form for assistance in filling them out call VAERS at 1-800-822-7967 or visit the VAERS web site at.

How can I find additional information?

To find additional information on the VAERS program and vaccine information, visit the FDA website at.

VAERS does not provide specific vaccine information, the Center for Disease Control (CDC) has a vaccine hotline to answer questions related to vaccines and immunizations. The CDC Vaccine Hotline is 1-800-232-2522.

Appendix III: Public Comment

Public Comment from Dr. Alan Lifson, MDH on the Vaccination Report:

1. Concerns about the use of the phrase "growing pains" in the first paragraph of the Introduction, page 2. Want to assure the public that the vaccines are thoroughly tested before release.
2. Two updates on information regarding the ACIP on page 3: the first is that the ACIP's recommendation to make Hepatitis A vaccination universal for all states with an incidence of 20/100,000 or greater was finalized. Second, a thimerosal-free Hepatitis B vaccine has been formulated and is recommended for use by the ACIP.
3. Comments that the key issue to the high MN incidence for Lyme Disease is its distribution (page 5).
4. Bottom of page 5: concerns that it appears as if previous uncomplicated Lyme disease is a risk factor on its own. In fact, it is more this in combination with geographical and behavioral risk factors.
5. Page 6, comments that a big problem with Lyme Disease vaccine is that it is not recommended for children under 15, and that this group is actually generally at very high risk for contracting the disease.
6. Generally concerned about the entire Rotavirus vaccine section and its applicability in light of its recent withdrawal by the CDC as well as the withdrawal by the manufacturer.
7. Page 12: worth highlighting further the fact that children are big source of Hepatitis A transmission because they are usually asymptomatic.
8. Comment on page 12 that the Favorable Category for the Hepatitis A vaccine (the IOM rating) would maybe be dependent upon the rate of infection in the immunized population.
9. Concerns about the accuracy of the recommendations for revaccination with pneumococcal vaccine on page 13.
10. Comments generally that there is controversy over whether the pneumococcal vaccine is effective against pneumococcal pneumonia.
11. Mentions limitations of VAERS- for example, just because an adverse event comes after the administration of a vaccine, the vaccine isn't necessarily implicated. Public Comment from Dr. Alan Lifson, MDH on the Vaccination Report.

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IV. Title: An Open, Multi-center Study to Evaluate the Safety of a Recombinant DNA Expressed Protein Vaccine for Lyme disease in Subjects Previously Enrolled in Lyme 008. 215274/016 (Lyme 016)

Invitation to Participate and Description of Project

You (your child) are (is) invited to continue to be a subject in a research study of an investigational Lyme disease vaccine being conducted at Yale University School of Medicine to determine the safety and immunogenicity (antibody response) of the vaccine when three doses are compared to four or five doses of vaccine.

In order to decide whether or not you wish to continue with the extension of Lyme 016 study, you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Background

You have previously received four doses of the vaccine from 1997 to 1998 in an investigational Lyme disease vaccine study (Lyme 016). The Lyme vaccine provided moderate protection against laboratory confirmed Lyme disease cases in the first year, and protected against most of the cases in the second year. Study results are still pending regarding whether the administration of a third dose of vaccine, given in the first year, increases protection. Also, the safety data of giving four doses of vaccine is pending analysis.

Purpose

This is a medical research study. The purpose of this extension of the study is to monitor the safety and immunogenicity (antibody response) of the investigational Lyme vaccine from the group of subjects who received doses on a 0, 1, 2, 12 month schedule for the purpose of determining the need for a fifth dose.

Description of Procedures

There will be a total of four or five study visits conducted during a 13 month period of time. Your total participation, including the previous months you have been enrolled, will last approximately 37 months from your first dose of vaccine.

The study will involve the following procedures: A brief medical evaluation will be performed at all visits. If a fifth dose of vaccine will be administered and you are female still capable of conceiving a child, then a urine pregnancy test will be performed at Month 24 Visit prior to administering the fifth dose of vaccine. A blood sample (approximately two teaspoonfuls) will be taken at all study visits (Months 18, 24, (25 to be determined), 30, and 36). This is to measure antibody levels. You will be given the following study materials at the time of vaccination: diary card, thermometer, and reaction measurement gauge and you will be provided with information on how to complete the diary cards. The diary card will ask questions about local and general reactions. The local reactions of interest will be redness, swelling and soreness. The general reactions of interest will be fever, headache, fatigue, arthralgia and rash. There will also be space for any other symptoms experienced or medications you may have taken.

Risks and Inconveniences

To date, approximately 7100 subjects have received at least one dose of the investigational Lyme vaccine. The majority of subjects were assigned to receive 3 doses of investigational Lyme vaccine. Therefore, there are limited data from subjects who have received 4 doses. The majority of subjects experienced soreness at the injection site. Other injection site local symptoms such as redness and swelling were reported, but with a lower frequency than soreness.

The most frequently reported general symptoms have been headache and fatigue; however, these events were also common in the placebo group. Other common general symptoms have been fever, chills, influenza-like symptoms, muscle pain, joint aches and rash. The majority of symptoms were considered as "mild to

moderate" and limited in duration. There was no increase in reports of general reactions after subjects received their second or third doses.
In the adult trial, over a two year period of time, a small percentage of both vaccinees and placebo recipients developed arthritis. There was no evidence that the vaccine recipients developed arthritis more often than the placebo group. However, the theoretical possibility still exists that the vaccine may cause arthritis in certain genetically susceptible individuals.

Another potential risk in this study involves the risks associated with drawing blood, including pain, bruising, bleeding, or infection at the site of the blood draw. The risk of introducing an external germ into the vein is extremely minimal due to the high antiseptic precautions of the standard medical practice. Approximately 10 cc (two teaspoonfuls) of blood will be drawn at each study visit.

As with all vaccines, there is a risk of allergic reactions, including rash, difficulty in breathing, shock and death.

It is possible that additional side effects remain to be discovered and long term effects of the vaccine are unknown. If, during the course of the study, new findings related to the safety of the vaccine are discovered that could affect your willingness to participate in this study, this will be disclosed to you.

Women should avoid pregnancy during vaccination and until 2 months after the last dose is complete because no information is available concerning the effect of this investigational vaccine on a fetus.

We request that during the study you do not receive some other vaccine (for example a flu shot) within four weeks before or after each injection.

Pregnancy
Since we are not sure that the Lyme disease vaccine is safe for pregnant women or their fetuses, we must be sure that you do not become pregnant during this study. All women of childbearing potential will be asked to have a pregnancy test within 30 days prior to any Lyme vaccine dose. Women will have to tell us what method of contraception they plan to use. We cannot accept you as a subject unless your plans to prevent pregnancy are acceptably secure. During this study, if you do not follow your plans for contraception exactly, or you think that you might have become pregnant, please let the principal investigator know this immediately, and you will not receive further vaccine doses.

Benefits
There is no guarantee or promise that you will receive any benefits from this study. You may receive protection against Lyme disease. It is not known, however, how long that protection will last.

Your participation may increase our understanding of the Lyme vaccine that may help others in the future. Your participation may also benefit others if a safe and effective vaccine can be licensed as a result of this research.

Alternative Treatments
There are no approved vaccines to prevent Lyme disease and you must assume that you are at risk of infection if exposed to Lyme disease. Simple protective measures such as wearing protective clothing outdoors, regular inspection of your body for ticks aand their prompt removal, and seeking early treatment if you develop Lyme disease should still be used.

Confidentiality
In all records of the study you will be known only to the researchers. SmithKline Beecham, the manufacturer of this vaccine, may inspect your study records, and the Food and Drug Administration may also look at your records. Your name will not be used in any scientific reports of the study.

In Case of Injury
If you become ill or injured as a result of your participation in this clinical study, medical treatment will be provided and the reasonable costs of such treatment, beyond those paid by your insurance, will be paid by SmithKline Beecham. No additional financial compensation for injury is available.

Voluntary Participation
You are free to choose not to participate, and if you do become a subject, you are free to withdraw from this study at any time during its course. If you choose not to participate, or if you withdraw, it will not adversely affect your relationship with the doctors or Yale-New Haven Hospital. Your doctor may withdraw you from the study at any time if he/she feels it to be in your best interest. If you should withdraw yourself voluntarily from the study or are asked by your doctor to leave the study, you will be asked questions about your experience with the study vaccine. You may also be asked to cooperate in having whatever laboratory tests and physical examinations your doctor considers necessary.

Questions
We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully - - as long as you feel is necessary - - before you make a decision.

Authorization: I have read this form and decided that _____ (name of subject) will participate in the project described above. Its general purposes, the particulars of involvement and possible risks and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Signature: _____
(parent/guardian if a minor)

Relationship: _____

Date: _____

Signature of Principal Investigator: _____ Phone 800-280-1097
or
Signature of Person Obtaining Consent: _____ Phone 800-280-1097

If you have further questions about this project or your rights as a research subject or if you have a research-related-injury, please contact Robert T. Schoen, M.D. at (800) 280-1097.

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HIC Protocol No. 9410

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[728] DELAYED AND IMMEDIATE RHEUMATOLOGIC MANIFESTATIONS ASSOCIATED WITH RECOMBINANT OSPA VACCINE.

Carlos D Rose, Paul T Fawcett, Kathleen M Gibney Wilmington, DE

Potential arthritogenic effects of OspA vaccination were the concern of investigators once AA homology between OspA and LFA-1 was demonstrated. Extensive field trials failed to show increased frequency of arthritis among vaccinees. We suggested that the less than universal level of protection and intense "seropositivity" among recipients would complicate interpretation of serologic data among vaccinees with rheumatic symptoms. We suggest the following scenarios as potentially challenging for clinicians: A-Vaccine induced arthritis; B-Lyme arthritis in a vaccinee; and C-Arthritis of other origin in a "seropositive" vaccine recipient. We report herein 4 cases of rheumatic symptoms in vaccine recipients. Cases 1 and 2 were identified among 21 adult volunteers in a prospective *LYMErix* vaccine trial. Cases 3 and 4 are children seen for arthritis who were participants of a Phase III clinical trial. Cases 1 and 2 were adult males who developed acute disabling small and large joint symmetrical synovitis and myalgia within 48 hours of the 2nd dose of *LYMErix*. In both cases disease was self-limited, required moderate doses of NSAIDs and resolved without sequela within 7 days. Case 3 is a 16 year-old male who presented with monoarticular knee synovitis 4 months after the 3rd dose. His serology at the time revealed antibodies to 93, 66, 41, 31, 30, 28 and 21 kDa antigens on IgG and 93 and 41 on IgM. Because of difficulties differentiating scenario A from B he received a full course of doxycycline therapy. Four months later he was asymptomatic. Case 4 is a 10 year-old male who developed bilateral knee synovitis a month after dose 3. Over the ensuing 5 months he developed intermittent asymmetrical oligoarthritis of knees, ankles, elbows and PIP joints at roughly monthly intervals. His serum 5 months post-vaccination revealed antibodies to 93, 69, 66, 64, 54, 53, 41, 39, 31, 30, 28, 26, 25, 22 and 21 kDa on IgG and none on IgM. He was noted to carry HLA DR4. Again because of the possibility of scenario A vs. B, a full course of antibotics was prescribed. Two months later he was asymptomatic. **COMMENTS:** Cases 1 and 2 confirm the arthritogenic, albeit transient, effects of OspA vaccination. Case 3 and 4 are likely delayed vaccine induced arthritis, although in Case 4 the extent of the immune response suggests either current or past *B. burgdorferi* exposure with disease re-activation induced by the vaccine. In addition, both cases illustrate the difficulties in interpreting Western blots in vaccine recipients. Atypical clinical manifestations, the presence of DR4 and the extent of the immune response make Case 4 intriguing.

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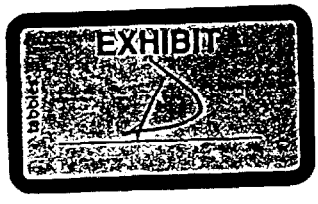

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News Release

June 7, 2000

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State officials recommend using combination of strategies to prevent Lyme disease, other tick-borne illnesses

Only some parts of state pose high risk of exposure, officials say

As they have in past years, state health officials continue to recommend that Minnesotans use a combination of strategies to protect themselves against diseases transmitted by ticks.

In some parts of Minnesota, there is a high risk of exposure to three different tick-borne diseases. In addition to Lyme disease, the list also includes human granulocytic ehrlichiosis (HGE) and babesiosis.

All three illnesses are carried by Ixodes scapularis—the "deer tick," or "black-legged" tick. Deer ticks are found primarily in wooded, brushy areas, in east-central Minnesota and portions of southeastern Minnesota.

Although the option of getting vaccinated against Lyme disease has received a great deal of attention recently, health officials are cautioning people that they need to take other preventive measures as well. At the same time, state officials also believe that many Minnesotans may have an exaggerated sense of the risk they face from these diseases, based on the false impression that the entire state is a 'hot spot' for Lyme disease.

The vaccine is only one part of a well-rounded strategy for protecting yourself from tick-related illnesses, according to Dr. Alan Lifson, who heads the Acute Disease Prevention Services Section at the Minnesota Department of Health (MDH).

"Right now, we don't have a 'magic bullet' for protecting people against these diseases," Dr. Lifson said. "We recommend that people use a combination of preventive measures if they plan to spend time in places where deer ticks might be present. They need to take steps to protect themselves from tick bites, and they also need to be alert for possible symptoms. For some people, the vaccine may provide additional protection. And if you've had the illness before, you should be aware that getting the disease does not make you immune."

The vaccine has some limitations, Dr. Lifson noted. It doesn't offer any protection against HGE or babesiosis, and it isn't approved for use by people under the age of 15 or over the age of 70. In addition, to get maximum benefit from the vaccine, you need to get a series of three shots. The first two shots are given a month apart, and the third shot is given 11 months after the second.

Based on clinical trials conducted by the manufacturer, the vaccine appears to reduce your risk of getting Lyme disease by about 50 percent after the first two shots, and about 75-80 percent after you've had the third shot. Research has been underway at MDH to assess the vaccine's effectiveness for people who may have been exposed to

EXHIBIT E

Lyme disease in Minnesota.

Anyone considering vaccination should consult with their physician. Not everyone is at risk of developing a tick-related illness, Dr. Lifson emphasized. For that reason, not everyone needs to be concerned about getting vaccinated, or taking other preventive measures.

"The 'high risk' designation only applies to a few parts of the state," he said. "And even if you do live in one of these areas, you're only at risk if you spend time in places that provide good habitat for ticks -- primarily wooded, brushy areas. It's very unlikely that you'll be exposed to ticks in your own back yard, unless there's suitable tick habitat close by."

Almost two-thirds of the people who get Lyme disease in Minnesota are exposed to the illness in a handful of counties. Those high risk counties include Aitkin, Anoka, Cass, Chisago, Crow Wing, Isanti, Kanabec, Mille Lacs, Morrison, Pine, and Washington County, the southern portions of Carlton and St. Louis County; the eastern portions of Houston, Wabasha and Winona County; and northern Ramsey County. Most of the Twin City metro area lies outside this "high-risk zone."

Another fourth of Minnesota Lyme disease cases occur in people who were exposed in western Wisconsin, and about seven percent occur in people who were exposed elsewhere in Minnesota.

Deer ticks are most active between April and September. They are smaller than the common wood ticks that are most active during the early weeks of summer, and they lack the wood tick's characteristic white markings. Deer ticks are darker in color, and the female has a reddish appearance.

Health officials recommend the following measures to help prevent tick exposure:

- Avoid possible tick habitat whenever possible. Use a good tick repellent, and follow the manufacturer's directions.
- Wear clothes that will help to shield you from ticks – for example, long sleeved shirts and long pants. Tuck your pants into the top of your socks or boots, to create a "tick barrier."
- Check frequently for ticks, and promptly remove any that you find, using a pair of tweezers or tick forceps. Be aware that folk remedies like vaseline, nail polish remover or burning matches are not a safe or effective way to remove ticks.

If you do develop a tick-related illness, you should see a physician as soon as possible. Early symptoms of Lyme disease typically include a characteristic "bulls-eye" rash, consisting of a reddened area with a clear area in the middle. The rash may expand in size to cover a very large area, or even appear in several places on other parts of the body. The rash doesn't develop in everyone who gets Lyme disease, however. Other early symptoms of Lyme disease can include fever, headache, fatigue, chills, and pain in the muscles or joints.

Symptoms of HGE can include a fever of 102 degrees or more, chills, shaking, severe headache and muscle aches. Babesiosis is characterized by a high fever, chills, headache, muscle aches, fatigue, and loss of appetite.

Over 2,500 cases of Lyme disease have been reported in Minnesota since 1982, including 283 cases last year.

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