medicated, but I still have trouble with my hands. I continue to experience pain in other joints, such as my elbows, my knees, jaw, neck and feet, and I'm usually fatigued.

Previously I was healthy and energetic, routinely taking only calcium and vitamins. Only after experiencing this adverse reaction did I learn that there had been concerns expressed about the safety of the vaccine, particularly related to the genotype HLA DR4, for which I have since tested positive.

This information most certainly would have enabled us to more realistically judged the relative risks and benefits of taking this vaccine.

If we had still believed the vaccine worthwhile for us, I could have had the option of genetic testing to avoid a problem, rather than in response to one.

The lack of disclosure of this information had further ramifications for our family. After I became symptomatic, my son was still due for his third injection. To determine whether he should complete his series, I consulted the chief of infectious disease and travel medicine at Northwestern.

Because the concerns about a possible

genetic vulnerability apparently had not been shared with the wider medical community, this doctor believed my adverse reaction was an idiosyncratic response to the vaccine that would have no bearing on my son's health.

I then consulted a physician at Tufts, more familiar with the vaccine, who advised against giving LYMErix to my son. Fortunately Jason had not had the third shot. Imagine how awful it could have been had Jason followed my path.

It is apparent that LYMErix, an entirely optional measure intended as a preventive intervention has harmed me physically, emotionally, financially, and has negatively impacted the life of my family.

My daily functioning remains compromised. I lack the ability, the energy to maintain my former level of activity and commitments, my ability to work, volunteer in the community, and share activities with my children has drastically diminished.

I was only trying to be diligent about my family's health. And as a result I now have a health problem for which no effective solution may exist. I am faced with such diagnostic possibilities as untreatable autoimmune disease arthritis, or an activation of a previous exposure to the lyme

bacteria.

There are few acknowledged experts regarding this reaction, and no widely accepted treatments. It seems to me that when evaluating the vaccine the possibility of adverse reactions of unknown duration, having no known cure, should receive greater weight than those potential reactions with well understood treatment protocols.

My husband and I have always had great confidence in the FDA's approval of medications and its communication with the medical community. We expected that all information which physicians might reasonably need to make recommendations concerning our health would be made available to them.

We were not informed that this very group expressed reservations which were not disclosed in the manufacturer's literature. We had no idea that there were unresolved safety issues requiring further study, and that by taking this vaccine our family would unwittingly become subjects of an ongoing drug trial.

Doctors and their patients need to be given complete disclosure of a possible risk, as well as the claim benefits. Only then can they make prudent decisions together.

We hope that others will have the benefit

of all of the information necessary to make well considered choices.

This morning I was thinking about your sources of data. Last May, when the nurse at Northwestern called SmithKline to report my arthritic reaction, and to seek information, she was told that there were no problems, just anecdotal reports.

They requested no further information about me. The nurse told me that she did not find SmithKline helpful, or concerned.

I thank you for this opportunity to share my experience. Thanks for your attention.

CHAIR DAUM: We thank you for your effort, and your experience. We would like to call on Ms. Linda Scharf-Lurie next, with Terry Elias following, and then a letter will be read on behalf of Nancy Vroon by Jenny Marra. Ms. Lurie.

MS. SCHARF-LURIE: Good afternoon. My name is Linda Scharf-Lurie, and I have been asked to speak on behalf of my daughter Vanessa.

Vanessa had a pretty normal childhood and adolescence until the year 1999. She had a horse that she used for exercise and enjoyment. She had competed on him in various venues. They enjoyed jumping and dressage.

She volunteered at a therapeutic riding barn, and worked with multiply handicapped children. Her plans were to get her degree in veterinary medicine, and have a small animal practice. She held down a job at a vet's office, and loved going to work and facing the challenges there.

In the spring of that year I decided to get her the lyme vaccine. She was in contact with various animals daily, and spent a lot of time in the woods with horses. It seemed like a good idea at the time.

She had had a simple case of unconfirmed lyme disease when she was around 12 years old, and it seemed to respond to antibiotics, so I thought LYMErix would be a good idea.

My primary doctor looked over the literature, and agreed to give the series of injections. Our lives have never been the same.

After the second injection Vanessa complained of ankle pain. I took her to an orthopedic surgeon who couldn't find anything wrong at that time. We sent her for physical therapy and gave her medications. She made the best of it, and never really got much better.

She had vague complaints about her joints

bothering her, but again she kept plugging along. She developed flu-like symptoms, a rash, and woke up on October 31st, 1999, with peripheral blindness.

She was having terrible muscle aches and joint swelling and pain. We went to many specialists. She had a spinal tap, an MRI, Gallium scan, multiple blood tests, including PCRs for lyme, all negative.

Finally we decided to test her for HLA DR4 and lo and behold we had a positive. We also had a positive ANA.

To this day she continues to test negative for lyme, MS, lupus, Kroen's disease, and all of the other autoimmune illnesses that our doctors assumed were the possible cause.

There is no history of juvenile arthritis in either side of our family. Her arthritis just kept getting worse, even with treatments of anti-inflammatories, and all of the arthritis medications on the market.

She spent her entire senior year at home, too ill to even walk through the hallways, and put in a full day at school. She missed her senior prom, and any social activities that a normal senior in high school participates in.

Her horse could not be exercised, or

jumped by her, for a very long period of time. We have taken Vanessa to many specialists in the New York and New Jersey area. They have no explanations for this sudden dramatic change in her health, except the probability that she had a reaction to LYMErix, which somehow caused an autoimmune reaction because of the body's exposure to OspA.

I'm not as knowledgeable as this distinguished panel of experts that I speak to, today. But I know one thing with all of my being. It was LYMErix which somehow had this devastating effect on my 17 year old child.

I think you have all considered that possibility before today. Maybe after today you will think it is more than just a possibility. You will see that this drug can have some long-lasting dangerous side effects.

Just remember, I have been told this by many a doctor in the last year and a half. They can treat and often cure lyme disease, but they cannot cure an autoimmune arthritis.

This is an 18 year old who will never again be able to run to catch a bus, jump her horse with abandon, her life will be forever changed by LYMErix. Please consider this very carefully when

making your decisions about continuing keeping this on the market and giving it to children.

CHAIR DAUM: Thank you very much, Ms. Lurie. Ms. Elias, then a letter to be read by Ms. Marra followed by David Weld.

MS. ELIAS: You had it right the first time -- Elias.

CHAIR DAUM: Elias. I'm sorry.

MS. ELIAS: That's okay. I'm a health care professional licensed in the State of Maryland. I'm also a survivor of Lyme Disease. I am also a recipient of LYMErix Vaccine.

I'm not real sure how many people have received the vaccine. If you haven't I challenge you to. Knock yourself out. I'll give you my third dose. It's in my refrigerator. Anybody want it? I don't.

I survived Lyme Disease by sheer determination. I stand here today by shear determination and a good dose of Arthrotac.

They told me I didn't have Lyme Disease. They told me my child didn't have Lyme Disease. When I presented to my doctor any possibility that I had any problem from the LYMErix vaccine, she jumped down my throat -- literally. I left that office in tears because the HMO's, number one, didn't want to pay for

my first two shots.

Number two, they don't want to recognize it. They don't want to get involved. Because you know what, they just might have to do a little more paperwork. And then they may have to say you know what, we really shouldn't have given you that shot the day you walked into our office with a flaming infection from a tick bite that was bigger than the size of my hand.

But you know what, I was told that it was totally safe. I don't think so. I looked through any FDA file I could find. I combed Smith Klein & Beecham's files, anything, any kind of medical information I could get my hands on.

Dosage calculations, contraindications, you name it I did it. There's absolutely nothing. And I'd like to question something a lady asked before. Have you changed any information that you're giving to the public? No you haven't changed a thing.

They're still giving the vaccine. There is no information in any of it that says, do not give it if you have a current infection. My doctor told me it was totally safe. No it's not.

I was almost going to get it for my 18-year old daughter who now has Lyme Disease, that I

kept telling them that she had. Not on a bet. I'll take her to any Lyme Disease literate medical doctor in the world before I would ever consider giving her that vaccine.

And I work in the private duty sector. But I live in a small endemic community in backwoods nowhere U.S.A.

I drive two hours to go to work on a private duty case that I love. I almost gave up my job because everybody kept saying no, no, no, no, no, no, no, no, you're wrong. And if not for fighting back, like everybody else has, where would we be.

I challenge you all. Go to your doctor. Get your first shot. I dare you. Thank you.

CHAIR DAUM: Thank you Ms. Elias. We call next on Jenny Marra to read a letter on behalf of Ms. Nancy Vroon who apparently couldn't be here today.

MS. MARRA: No. She's in a wheelchair in New Jersey.

CHAIR DAUM: Okay. And then we'll ask David Weld and then Pat Easton to speak following. Ms. Marra, please.

MS. MARRA: She writes, To Whom It May Concern. I am unable to attend the January 31st FDA Vaccine Advisory Committee meeting due to a

restrictive condition, Transverse Myelitis, resulting from the LYMErix Vaccine.

In the Spring of 1999, I decided to get the series of LYMErix shots after viewing a very convincing T.V. commercial touting the importance of protecting oneself from Lyme Disease.

I felt this would be a good thing to take advantage of since I had had numerous bites from ticks which cause Lyme Disease.

I was given the first shot of the series on April 20, 1999. Thirteen days later I collapsed completely paralyzed. Many tests at the hospital confirmed the diagnosis of Transverse Myelitis, inflammation of the Myelin Sheath around the spinal cord.

After days in Intensive Care at the hospital, I was transferred to the rehabilitation center where I spend six months. After intensive physical and occupational therapy, some mobility returned but I am in a wheelchair most of the time. My life has been drastically changed for the last 21 months.

Up to the day I collapsed, I was constantly on the go with meetings of historical societies, community organizations, church activities,

house tours, dinner parties, exercise classes, bus trips, theater outings, concerts, etcetera.

I used to wear my daughters out just telling them about all of the running around I did. I used to be a world traveler, but now because of the physical limitations I stay close to home.

I am able to live at home only with support from family and friends and a paid nighttime caregiver. For the first nine months, after coming home from the rehabilitation center, I required round-the-clock caregivers.

Prior to the LYMErix Vaccine, I was in excellent health, completely independent. I strongly urge you to take LYMErix off of the market to spare others the pain and suffering it may cause.

Very truly yours, Nancy Vroon.

CHAIR DAUM: Thank you very kindly, Ms.Marra. David Weld is next, then followed by Pat Easton and Dr. Kenneth Dardick.

MR. WELD: Good afternoon. I'm David Weld, Executive Director of the American Lyme Disease Foundation. Our organization does receive some unrestricted grant monies from Glyco Smith Klein which helps to support our overall programs and services.

Let me make it clear that it is the

foundation's policy to maintain a strict scientific standard as a basis for all information we disseminate.

The American Lyme Disease Foundation is dedicated to promoting Lyme Disease prevention, diagnosis and treatment through educational programs and services.

As a liaison between the public and medical research institutions, the Foundation provides easy access to key information that allows people to make wise health care decisions.

In particular we stress the importance of prevention and early intervention in avoiding complicated, expensive, and potentially debilitating long term illness.

Our efforts are derived from the principle that a clear understanding of lyme disease risk, and how to reduce it both diminishes the fear associated with the disease, and results in proactive precautionary behavior.

In addition we believe that lyme disease prevention techniques must target not just people, but ticks as well. As purveyors of a potentially debilitating disease deer ticks represent an almost universal threat in highly endemic areas.

Deer tick population reduction is certainly one of the cornerstones of lyme disease prevention research. To this end the Foundation support research focusing primarily on new tick control methods with potential for commercial application, and in the last year provided over 100,000 in funding for such projects.

It is our hope that a greater understanding of tick population dynamics, tick host interrelationships, pesticides susceptibilities and other factors will enhance progress in the area of tick control.

A third approach to lyme disease prevention involves the transmission blocking method exemplified by LYMErix, the subject of today's discussion. I am not here today to argue in molecular detail the safety of the vaccine.

I will leave that task to those more directly involved in the supporting research. Let me be clear about lyme disease prevention. No one method, including the vaccine, is completely effective all the time.

The CDC, NIH, Public Health Department, research agencies and the Foundation all recommend that prevention be viewed collectively. With

accommodation of precautions, including daily tick checks, the use of repellents, habitat modification and others to be taken in tandem.

I will end on this note. Science has much yet to discover about lyme disease. It does not, by any means, have all the answers. As a father of a young daughter who failed to respond completely to standard early lyme disease treatment, I have been faced with a dilemma that every parent in my position experiences, what next.

I speculated that science might not help my daughter in this case. But despite its flaws the scientific method is the best we have. It is structured to effectively eliminate subjectivity in a controlled environment.

Any anecdotal evidence pertaining to LYMErix or any other vaccine which may be developed, until subjected to rigors replicable study is of limited value in assessing the vaccine's merit, and in determining policy relating to its use.

Thank you.

CHAIR DAUM: Thank you sir. And I hope you catch your plane. We have Pat Easton followed by Dr. Kenneth Dardick.

MR. EASTON: Thank you for allowing me to

speak here today. I'm here representing my wife, Carol Sue.

My Susie is 17 years younger than I am, and until two years ago she could run circles around me, and out-think me. All that has changed.

Let me give you a brief history. In 1998 she had an operation on her back, a bad disc. But during that, and before that operation she was thoroughly checked out, head to toe, because the doctor didn't want to proceed if there was any indication of arthritis.

She had a head to toe check out, no arthritis whatsoever. She went through that operation, remarkably she was doing everything she should in that summer of 1998.

In November of 1998 we moved from the 95 beltway, 250 miles northwest to the mountains of Pennsylvania, got a new HMO, new doctors, the whole thing. That was in November. In about the February time frame both of us went in to our new HMO and did the head to toe check out, both of us, complete physical, nothing wrong with us.

At that time it was suggested to us, since we were going to live in the woods, and work in the woods, and what have you, that LYMErix was the way to

go. We both took it.

She noticed some pain off the first shot, but for her, I teased her and said, that is typical. When you get the flu shot you always get a mild dose of the flu, you know, that is you.

And she took the second shot, and immediately thereafter started all the symptoms that you heard many, many times over.

I would like to add a few other ones. She is now deteriorated, her eyesight is going. She is losing her mental capacities, too. It is a little tough. For a woman that I was worried on how I was going to keep up with as a 60 year old, it is hard for me to lay in bed beside her and hear the whimpers that she tries to turn -- excuse me.

On your reporting system, your VAERS reporting system, it took me 18 months to find it. She isn't even in your thing. We finally got to it, found a copy of it and mailed it in. I have to admit the people that phoned back were very, very cordial, very helpful, and spent a lot of time with my wife.

But your reporting system might do well in the beltway, but out where the ticks are, out in the hinterland, nobody knows about it, or they are not telling you.

Out in the sticks, and out in the hinterland the doctor, God love her, she tried everything. We have been diagnosed from everything that you ever imagined, down through lupus, tested for and come up no. Because she couldn't believe in her heart that it was the lyme vaccine because she said there is no indication -- she is upset to this day because I brought her from other sources.

And she said, why didn't they have that down there, Pat? I apologize, I'm sorry. But she is still upset because she doesn't have the information from you, she had to get it from me.

Thank you, sir.

CHAIR DAUM: We thank you, Mr. Easton. Dr. Dardick is our final speaker of the afternoon. Is Dr. Dardick here? I think probably not.

Are there other people who wish to come forward and speak for five minutes, that haven't made themselves known to us. I see one hand. Would you come to the microphone and identify yourself, please? And this will be our final speaker.

MS. BURKE: Hi, my name is Karen Burke. I wasn't planning on speaking, I have no prepared, anything to say. We are here because my husband had the LYMErix vaccine two years ago, actually a year and

way to the liver, toxic.

Prednisone, which as we all know can cause osteoporosis, they are finding that now, particularly in males, from what I understand. Anyway, we are not able to conceive any more children until he is off these medications.

Will he ever be? You know, the standing joke is, I love to kid around, right now I wasn't planning on being up here, I didn't realize I could speak. If I knew it, I would have been prepared. I am like a nervous wreck, you can hear it in my voice.

But my standing joke with him is, honey, at least when our kids are big enough and by that point you will probably be on a wheelchair, and you will get us on the rides quicker. Well, you know what, that is a joke, it is not funny, but you have to have some fun in your life.

And it is not anymore. He lost his business, he has no more construction business, done. Pretty much a desk job. Thank God he has a job, thank God I have a good job.

The point is life has changed, and is it ever, ever going to be the same? I truly, truly believe it came from the LYMErix vaccine. As someone said before, I mean, I know it is not for me to ask

you guys questions. How many of you people have it, the vaccine, how many of you people would give it to your loved ones?

And if you did, you wouldn't be sitting where you are right now.

I really, really believe it came from LYMErix vaccine, just as everyone else has said. Our life has been turned upside down. Fortunately it is not something worse, fortunately it is not something that is going to kill him, or at least we don't know that it is.

So I just urge you to consider at least change the labeling, at least let people know that they have genes in their body, that if they carry this gene, in lay terms, they can go ahead, get tested to see if they have this gene before their life is ruined.

My husband does have the gene for rheumatoid arthritis. Never knew it. Perfectly healthy, healthy individual. Not any more, completely, completely changed. Functional after three or four o'clock in the afternoon? No. Where is he? On the couch. Is he sleeping? Yes, he is sleeping he is a mess. Two little kids, can't play with them.

The point I'm making is it is an awful, awful thing. If you went through it, all I can say is it is devastating, and it is awful, it has turned our lives upside down. Please consider not giving it to small children, or to anybody else, because do you guys finish your study, how many more people are going to be affected, how many more people are going to have this problem?

There is just too, too many to say it is coincidental, it is not. That is all I have to say. I'm grateful I had the opportunity to come up here, I wished I would have called and made arrangements to speak.

I'm done being a nervous wreck, I'm glad I got my point of view out. That is it, I'm going to go sit down and get some water.

CHAIR DAUM: And thank you for taking the time to share your thoughts with us.

I have to tell you, sitting up here as a physician, that the stories and the thoughts that were shared with us this afternoon can't help but be profoundly moving.

And I can assure you, on behalf of the committee, that your views, your thoughts, your energy and time taken to share your ideas with us today, will

be taken into account in our discussion and deliberation.

I would like to now take a ten minute break, and then we will begin committee discussion. Thank you.

(Whereupon, the above-entitled matter went off the record at 3:08 p.m. and went back on the record at 3:24 p.m.)

CHAIR DAUM: Welcome back. We are now going to have the -- everybody sort of settle down, please. I know it has been a long day. We will try to get this done quickly so that we can get people on their way, and back to homes or activities.

The Committee will now deliberate the issue that is put in front of them by our colleagues at the FDA for discussion. And in this instance we are not going to have a direct vote on anything, but we are going to address this question, this issue.

Please discuss the safety data and the plans for continued safety evaluation of the lyme disease vaccine. Appended to that, I've just been told by Dr. Midthun, is that comments about what might or might not be done to the package insert, or the labeling are also welcome during this session.

What I would like to do is to first have

those members of the committee that wish to ask clarifying questions, or raise points, to feel free to do so for a while. When we get the sense that most of the points have been raised, I will then like to hear this issue of the FDA's spoken to by everyone at the table.

So we will begin by people who want to raise points that have come out of today's session, and we will try and get some discussion going on them.

DR. DATTWYLER: I will raise something.

CHAIR DAUM: Okay, then Ms. Fisher. Thank you.

DR. DATTWYLER: On the point of serologies, the original serology recommendations from the CDC panel were not in reference to western blots, they were using an infectious disease principle, acute and convalescent serologies.

And the idea was a standard rise in titer could be indicative of acute disease. And I think there was some misconception there that that was in reference to western blot, it was not.

The other thing is that the scientific basis of the CDC recommendations, as far as serologies, is not solely based on just the Dressler-Steere study. But, in fact, there were additional

studies carried out by members of the CDC Advisory Panel, and CDC itself.

So that has been validated through a number of different scientific studies.

CHAIR DAUM: Are you raising, clarifying issues with respect to understanding serology for us?

DR. DATTWYLER: Yes, that is all I am doing. And I can also say, as a member of that CDC committee, that the vaccines were never discussed in serologic meetings. So that there was no forethought about vaccine trials. We were solely concentrating on serologic issues at that point.

CHAIR DAUM: Thank you. Ms. Fisher, you had your hand up?

MS. FISHER: I had a question after Dr. Elkins presented, and I would sort of like to ask it to her, and also to SmithKline Beecham.

In light of the findings by Dr. Shell that at higher concentrations OspA protein there was an effect. The OspA vaccine preparation contains 30 micrograms of OspA protein, I understand. And the mice that were injected in the SmithKline Beecham study were injected with one microgram of OspA.

My question is, could the concentration of OspA protein affect the findings of studies in the

animals?

CHAIR DAUM: Dr. Elkins has just come into the room, and might not have heard your entire question, Ms. Fisher. Would you mind repeating it for us?

Dr. Elkins, this is a question for you and for the sponsor.

DR. ELKINS: I am sorry, what was the question?

CHAIR DAUM: Why don't you repeat the question, please?

MS. FISHER: The OspA vaccine preparation, I understand, contains 30 micrograms of OspA protein. And the mice that were injected in the SmithKline Beecham study, I think you said they injected one microgram of OspA. And I was wondering, in light of what you talked about with regard to Dr. Shell's work, could the concentration of OspA protein affect the findings of these studies?

DR. ELKINS: Well, I won't attempt to address the question from the SmithKline experiments with the mice. In the Wisconsin study they used three doses, 30 micrograms, 60 microgram, and 120 micrograms, 30 micrograms is the adult dose.

And, of course, a hamster is much smaller

than a person. The dose response in that study was not very well characterized. They did report that there was less of an impact on joint swelling after infection at the higher dose, the 120 microgram dose than at the 30 or the 60 microgram dose, which I think is probably counterintuitive.

Clearly there could be dose related effects, but how you would relate those between hamsters and mice, and adult vaccination, is very difficult.

CHAIR DAUM: Thank you. Does someone from SmithKline want to deal with that? Is Dr. Lobet here?

DR. LOBET: We believe that the use of such a high dose in hamsters is exaggerated, in a way, because it would represent something like, if you compare the body weight, 504 higher concentration than what you would use in humans.

Further, when injecting the hind paws, you are going to exacerbate an inflammatory process, because in this location it is known that an inflammation would take place. I mean, this site is prone to severe inflammation.

We use one microgram in our studies because we find this more relevant to the human situation, and closer to the human situation, as you

have seen in the past, using one microgram of OspA was the dose to approach the immune response seen against OspA in humans.

And we thought using one microgram of course would reduce the body weight, the concentration, as compared to the hamster study.

MS. FISHER: It is interesting that there is no dose adjustment for, you know, one day old infants versus adults in hepatitis B vaccine, so there is no dose adjustment there.

DR. ELKINS: There is probably another point that should be reiterated about the hamster study.

CHAIR DAUM: Go ahead.

DR. ELKINS: Which is that the recombinant OspA used in that study was produced by the investigators, it was no the LYMErix vaccine. And the investigators stated that it was a non-lipidated version of the protein.

Although that characterization data was not included in the paper, and the technique used to create the protein would have, from the description given in the paper, been just as likely to produce a lipidated protein. So there is some unanswered questions of exactly what the injected recombinant

material was, and how that might compare to the LYMErix vaccine itself.

DR. SNIDER: Could I just ask a follow-up? Did they use an adjuvant --

DR. ELKINS: Yes, they adsorbed it to one percent alum.

CHAIR DAUM: Dr. Griffin is next.

DR. GRIFFIN: I just wanted to comment, from an immunologic point of view we don't usually adjust doses in the same way that we adjust drugs, by weight. I mean, frequently, Ms. Fisher is right, the same amount of vaccine is given to a very small person, as to a large person. The same way with animals.

DR. LOBET: Sure. But in the case of mice we know that --

DR. GRIFFIN: In the case of mice.

DR. LOBET: In the study in the mice we know that we get the same immune response in humans with using one microgram.

CHAIR DAUM: Dr. Myers, then Dr. Ferrieri please.

DR. MYERS: I have two questions. The first one I would like to ask Dr. Ball. I know with VAERS it is very hard to make a comparison of apples

and oranges, and so on.

But there are 322 cases reported of arthritis, arthralgia, or arthropathy. And there were 44 that reported a severe musculoskeletal diseases. And the manufacturers told us that 1.4 million doses of vaccine have been administered.

And I realize that the comparison I'm going to ask for is not a valid one, but give us a sense of perspective.

Could you tell us of another vaccine that is directed at the same sort of age group, what type of VAERS report do you get in the same areas? For example, hepatitis B illuminating the pediatric administration, or some other vaccine?

Is there some way you could give us a feel for whether 322 and 44 is more than you would have expected, or DT would be another vaccine.

DR. BALL: I can't give you the numbers, I don't have that information. But I can tell you that we did look at reporting rates, where reporting rate is the number of events divided by an estimate of the doses distributed, and compared the reporting rates for various coding terms for LYMErix with hepatitis B vaccine given to adults, and also flu vaccine given to adults.

And what we see there is that for pretty much every coding term the reporting rate is higher for LYMErix. And then if you specifically look at the coding terms for joint related symptoms, the relative reporting rate, which would mean the ratio of the reporting rate for LYMErix, compared with the reporting rate for, say, hepatitis B vaccine in adults, is also higher, and it is a little bit higher than you see for non-specific coding terms, such as flu syndrome.

But, as you are saying, there are a number of caveats to those comparisons, specifically we know that for newer vaccines there is more reporting, and that is suggested by the higher overall rates for LYMErix.

We also know that media reports can influence reporting differently, for different vaccines. And we know that age and gender differences of vaccine recipients can also influence reporting. And although we have tried to account for that by just looking at reports in adults for hepatitis B and influenza, we don't have age and gender distribution for the actual vaccine recipients.

And it is probably different for people who receive flu vaccines, probably older, and probably

a little bit younger for people who receive hepatitis B vaccine.

So, overall, as a result we can't really conclude that an increased reporting reflects a causal relationship between the vaccine and the events for which the reporting rate is increased.

But it does focus our attention on those events. Now, in this case, we were already focusing on the arthritis reports because of the theoretical concerns. So it essentially reinforced that.

CHAIR DAUM: Thank you.

DR. MYERS: The second question I had really had to do with a post-marketing studies, and only 3,600, approximately 3,600 cases enrolled to date.

And given the enrollment problems with the fact that 1.4 million doses of vaccine have been distributed, I wondered what the manufacturer's plans were for trying to rapidly address the problem of getting the data.

CHAIR DAUM: Yes, I would like to hear the answer to that, as well. Does someone from the manufacturer want to take that on? Dr. Kahn.

DR. KAHN: I think this is a good time to call up Dr. Platt, in fact, to talk about that

specific issue, if I may. And at the same time I think it is fair to say the uptake of the vaccine is low, and we've often pondered this ourselves.

And there are a number of factors that we think of, is an adult vaccine a personal choice vaccine, it is restricted by geographical and, indeed, seasonal use.

And adults, unlike pediatric vaccine, where there are recommendations and plan visits, is quite a challenge to actually get the word out that this is available, and have adults come in of their own volition, and you see that.

And I think the negative press must have caused the attitude. It is an obvious thing. So maybe I can ask Dr. Platt about the plans for the future.

DR. PLATT: Part of the resolution is the addition of additional managed care organizations to this study, which is already in train, so that the cohort is actually two to three times larger than we were able to report.

That is, we will have the data from the beginning of 1999 for all three of the HMOs by the latter part of this year. I do think that it is important to recognize sort of what will exist at that

point, because it is because the information you get increases more or less as the square root of the number of cases.

Roughly speaking 5000 cases gives you about half the information that 25,000 cases will get. That is not to minimize the importance of getting as much information as possible.

But if, for instance we were at the end of three years of recruitment to have twelve and a half thousand cases, half the size we were expecting, we would have something on the order of 80 percent of the information that would come from a 25,000 member study.

So there really are, I think, two ways to approach this. One is to try to get the additional information that is already entrained, available as soon as we can. And for us that means later in this year.

And then I think to evaluate what we see in that. I think there would be -- I personally would have a very different response to seeing no excess in the immunized group versus a modest excess that we can't distinguish from random noise.

And we should be there, I think, by the end of this year. That would also, I think, be a time

when we could evaluate the prospects for getting other population based sources of information that might be able to contribute to this, either to this study, or a companion study.

DR. MYERS: Just a final question and I will be quiet. I take it from the answer, then, that the manufacturers are not planning on other studies, it is a one study post-marketing plan?

And are there other investigators that are going to increase the data base? Or is --

CHAIR DAUM: I'm not sure whether you are talking about -- are you expressing dissatisfaction that enrollment in this study is going slowly, or are you asking --

DR. MYERS: Well, I was asking if there were going to be other studies in addition, because this one is going quite slowly.

DR. PLATT: I don't mean to speak for the manufacturer on this. I will tell you that I have looked, fairly diligently, for potential collaborators who could contribute.

DR. MYERS: I didn't mean it critically.

DR. PLATT: No, I wasn't taking it critically. I'm just telling you that as an investigator who would like to see the study progress

more quickly, I have essentially on my own initiative, but with the knowledge of the sponsor, enquired of other potential participants.

And I'm unaware of any at this moment. It may be that by next year others that could participate would be willing to do it. But I have talked with, I think, all of the investigators who would be in a position to do this kind of work.

And they fall, basically, into two categories. Those who work in environments where lyme vaccine is not used very much, and those who just can't take on the commitment of doing the study at the moment.

DR. O'FALLEN: I am not sure I agree with the rather optimistic expressions of the kinds of power that we have after getting only half, or perhaps even only a third of the originally prescribed studies.

The standard error of an estimate is reduced by a factor of two only if you increased the sample size by a factor of four. So you really, I think, overstated what we will have available if we don't get a fairly substantial proportion of the original target.

And I'm not sure, as I said earlier this

morning, that I believe that you will get even as big a group as you think you are going to get, especially from the Minnesota group.

CHAIR DAUM: Dr. Coyle, did you have your hand up? Thank you, Dr. O'Fallen.

DR. COYLE: I actually had a question, and I was wondering, in the cohort study do you feel very confident that the problems similar are akin to what the patients were testifying to here, would clearly be picked up?

I'm wondering about the possibility of including something like a new pain syndrome to make sure that it is picked up. Do you feel confident that all of these patients that if they were in an HMO cohort, your HMO cohort would be picked up, would be detected?

DR. PLATT: My belief is that we would. We are providing to FDA a tabulation of all of the ICD9 codes that are submitted, not just the ones that are in that group that are called arthritis, and musculoskeletal.

So in the event that these syndromes would be coded outside those ICD9 codes, we would be able to see that signal, and FDA reviewers would see it as well.

So I expect that the kind of problems that require many visits to a physician for that problem are the kind that would likely show up as signals in a claims data base, even with all the problems that the claims data bases have.

Could I just return to the prior comment? Because I didn't mean to disagree with your statement about power. And I really do believe that recruiting the full cohort would be a desirable thing to do.

I just want to be sure that we have a common understanding that the information we received is greatest for the first cases, and marginally less for the later cases that are recruited.

We have preliminary counts from Minnesota, and I think that I'm giving you a fair estimate of the cohort size that we will have by the end of the year.

CHAIR DAUM: Thank you. Dr. Ferrieri, Dr. Estes, Dr. Diaz, Dr. Goldberg.

DR. FERRIERI: Thank you, Dr. Daum. A couple of brief comments, and then some sort of suggestions with, hopefully, response from the sponsors.

I chaired this committee in May of '98 when you presented data that led to our recommending to FDA that the product continue in the process for

licensure.

And you have heard everyone say that we had many reservations, and they are in all the documents that people have received. So I will not reiterate them.

But they have surfaced today from many people, and FDA knows what they are. And I think, honestly, that the sponsor has attempted to obtain data that would address our concerns.

But here we are, two and a half years later, and really aren't much further along. So the uneasiness that some of us had then, and there are at least two people at the table, perhaps other than I, who did participate on that occasion.

I think that the uneasiness then is duplicated today, because the same questions persist. And I'm worried that the clinical data are not going to be forthcoming, that they may be inconclusive, that is worse case scenario.

And because of the low uptake in receiving the vaccine, that we may not be able to arrive at that faster.

Now, it is quite possible that this is, basically, a reasonable vaccine that fills a niche. And at the time, you know, within five years, two and

a half years ago, there was great lay pressure and enthusiasm for having this licensed, for the lyme vaccine to be licensed.

So the expectation was that we would have those knowledge gaps filled, perhaps. But if we can't then I think we have to get back to the drawing board and try to attack this from a basic science point of view, and we need more basic research to help understand OspA, the gene, domains of the gene, perhaps.

I don't pretend to understand whether the epitopes for protection are different from epitopes that may regulate unfavorable reactions, and arthropathy, for example, or reactivation of something.

And, lastly, we might learn from the hamster model, perhaps, if we could manipulate the end result protein from a genetic point of view, and perhaps use the hamster model, we might be able to get to some of these questions that would be applicable to the human vaccination safety issues.

And earlier today we talked about the mice, and the lack of data to examine the administration of the OspA after vaccination. I'm sorry, the OspA after experimental infection.

But from the hamsters we've learned that the reverse is very intriguing as well, and that is OspA vaccination followed by experimental infection, that is out there for all of us, if we are exposed to the borrelia bearing tick.

So I would like you to seek out and get right to your corporate hearts and examine, how strongly you are attached to this vaccine, do you want it to be out there in the market? Because it is like a stock that is losing interest, you know, is this going to be the fate of Amazon.com?

I hope not, because you've put a hell of a lot of money into this. But you need to know how far do you want to go with it, how far are you prepared to go to unravel some of these very basic questions in addition to safety issues in human vacinees.

CHAIR DAUM: Thank you, Dr. Ferrieri, I think that was a very helpful comment for us all to hear.

I would like to go on with Dr. Estes next. Thank you.

DR. ESTES: I wanted some clarification about what studies, if any, are actually ongoing to look at the association between the HLA type and

potential reaction to this vaccine.

We were told this morning that the cellular immunity studies that have been completed were exploratory, and they were of limited power. And it is not clear to me that Dr. Platt's studies are going to address that.

Are there other studies that we don't know about that are planned, that are ongoing?

CHAIR DAUM: I'm going to ask the sponsor to address that, but I would also like to hear from FDA folks as to what they know that is going on that may have nothing to do with the sponsor.

But let's hear from the sponsor first.

MS. HOWELL: I'm Barbara Howell from the clinical research unit for Glaxo SmithKline in the U. S. And I just want to make one point with regard to the HLA typing pre-licensure.

You've heard, this morning, that there were basically two studies in which HLA typing was prospectively done. One of them was the lyme-008 study, which was the pivotal efficacy trial in which the HLA typing was done in conjunction with the cellular immunity study in a subset.

And as you heard, and as everybody agreed this morning, those studies were largely exploratory.

They don't support any association between arthritis and HLA type, but they don't definitively refute.

The point I would like to make is that in addition to that we know that in a large efficacy trial which involved more than 10,000 subjects, half vaccinated, and half placebo recipients, that study was prospectively designed to look at a comparison of musculoskeletal events, neurologic events in vacinees, as compared to placebo recipients.

And that based on the prevalence of the HLA DR4 allele in the general population we know that up to 30 percent of individuals then, both vacinees and placebo recipients, would carry the DR4 allele, and that there was no increase in musculoskeletal neurologic events.

We have been in discussions with the investigators of a phase IV study to explore whether or not we can look at HLA typing in the context of that study. We were concerned about delaying the start of the study proper because of considerations having to do with logistics.

One of the proposals would be that we could potentially look at HLA typing in vacinees who were exposed, and unexposed, who developed incident arthritic conditions, but perhaps do that only if we

do determine that there is an excess in the outcomes of interest, and that would be done further down the line, in the context of that trial.

Otherwise we do not have any other plans for HLA typing in humans.

CHAIR DAUM: Thank you, Dr. Howell. Would someone from FDA like to speak to, do they know whether anything is going on in this area? Dr. Ball?

DR. BALL: I just wanted to repeat what I said during my presentation, that the FDA is sponsoring a study. Initially it will be a survey of people who have reported joint problems to VAERS, and then once we obtain complete information on those cases we will identify arthritis reports and conduct a case control study comparing people who report arthritis after lyme vaccine, with people who report arthritis after other vaccines to VAERS, as well as people who report adverse events, other than arthritis after LYMErix to VAERS.

And in that study we intend to do high resolution HLA typing of all the cases and controls, and to compare the prevalence of rheumatoid arthritis associated HLA alleles in those groups.

We also propose to look at t-cell reactivity to OspA and LFA1 in those -- in the cases

in the control groups.

DR. FERRIERI: How many numbers do you project? I was confused, Dr. Ball, about this case control study. What are the projected numbers?

DR. BALL: Well, we know right now that we have about 133 reports of arthritic conditions in VAERS. We don't know how many of those will actually pan out to be true cases of arthritis.

So once we do our survey and obtain that complete information we will be able to identify the number of cases, and then we would match that with the different control groups.

My sense is that we will have something less than 100 cases. And so that the study is likely only to detect a fairly large effect at points present.

CHAIR DAUM: Does anybody know whether the -- thank you, Dr. Ball. Whether the NIH is interested in this? Because it sounds like it is some pretty basic immunology and microbial genetics to be done here.

And I wonder, does anybody know whether that has been declared to be a funded area for someone to be working on? If not we should probably get a sense from the committee that we think it is a pretty

important knowledge gap, and that we would like -- we appreciate the efforts of the sponsor and FDA, but would also like NIH to get to work on this as well.

Dr. Diaz, I think you are next.

DR. DIAZ: Dr. Ball answered one of my two questions, so thank you, I might come back to you later with a couple of other questions about the case control study.

But the other question that I had was in regards to the studies that are ongoing now, and your large HMOs. And we've had discussions today, in particular, and I likewise am concerned about the utilization of ICD9 codes, and what gets coded, etcetera.

I was just curious if any of the HMOs that are participating are going to participate in this study, by any chance, have any computerized data such as chief complaint, or triage data that could be looked at in addition, to try and mine for effects, perhaps, that may be associated with vaccination?

DR. PLATT: HMOs are largely quilts these days, made up of a variety of delivery systems. Harvard Pilgrim includes a multi-specialty group of about 250 to 300,000 that has a fully automated medical record.

And so those individuals are included in the data that I showed you. There we are not limited to the number of -- to the number of diagnosis allowed on a claims form. We search all the diagnosis that are used there.

So we have, essentially, the full automated medical record in that case. And health partners also has a more limited, a fraction of the health partners population I understand also has full, has automated medical record capabilities.

So for something on the order of 20 percent of the population that we are describing, there is more than just billing data that is available.

DR. DIAZ: If there is, that data might be useful to look at as a subset. Just to compare chief complaint and final diagnosis in terms of validity.

DR. PLATT: So we can subset that out, understand that we are, at the moment, looking at serious conditions as manifest by hospitalization there are very few events. So it will still be very few events if we look at a subset.

DR. DIAZ: I'm sorry, I misunderstood. So the data that you have, in terms of full medical record, is only for hospitalized patients?

DR. PLATT: No, I'm sorry, I didn't say that well. We do have, now, the full medical record data is only for the ambulatory care. That information is included in the data we gave you, and we can subset that out.

DR. FERRIERI: I'm from Minnesota but don't know health partners well enough to know how far along they are. But it would be my assumption they have a centralized data base now from all of their hundreds of clinics you would have everything feed into a central center, then, Rich?

DR. PLATT: We have access to all the data that health partners has, centrally. But health partners has a substantial part of health partners, I understand, about two thirds of it, is physicians basically in separate practice who don't have automated data.

So I think they too have sort of a two-tiered data quality configuration, in much the way that Harvard Pilgrim does for 20 percent of our population we know enormous amounts of information. And for the rest we have billing data, and my understanding is something like that is true for health partners.

CHAIR DAUM: Dr. Goldberg, please.

DR. GOLDBERG: Dr. Platt, the question that you just answered about the 20 percent of the population with complete data --

CHAIR DAUM: Would you speak into the microphone?

DR. GOLDBERG: The 20 percent of the population with complete data would speak to the kinds of questions that were being asked this morning for a substudy to compare the diagnosis there with their billing diagnosis, and then compare that to the total population.

You also said that 14 percent of your population turns over yearly at the Harvard Pilgrim. From the kinds of discussion that we heard this afternoon, if the complaints, or if short shrift is given to the complaints, these people might be more likely to leave the system.

I mean, have you thought about -- you talked about the fact that you would be unlikely to miss a diagnosis, a code that was recurring, or if somebody kept coming back, even if it wasn't in the first few visits it would be in a later visit.

If the patient was to be told this is not something we are going to deal with, which I'm hoping doesn't happen, you could lose that patient to the

system, completely.

Have you got some ideas about how you might address those sorts of issues?

DR. PLATT: I can say, as a general phenomenon, the member satisfaction data suggests that he members, in fact, by and large are very satisfied. And the turnover is actual bimodal. That is there is much more rapid attrition for new members, and then much lower attrition for members who have been -- for individuals who have been members for three years or so.

Much of that change in membership has to do with employee's decisions about the insurance company --

DR. GOLDBERG: I understand that.

DR. PLATT: So it is a complicated business to understand. And I think what we can do is provide basically sort of a life table analysis of the duration of membership after immunization, and even the number of visits after immunization, which I think would give us some sense of whether people are leaving soon after they are immunized, or whether they continue to have encounters for other diagnosis.

DR. GOLDBERG: I have a question for the sponsor. Given that the vaccine is --

CHAIR DAUM: Dr. Goldberg, I have a number of names lined up here, but why don't you go ahead. But let's try -- Dr. Goldberg will go, then Dr. Stephens, Dr. Luft, Dr. Manley.

DR. GOLDBERG: For the sponsor. I mean, given that the vaccine is really not out there massively, have you considered some kind of registration with each immunization so that you had developed a registry of vaccinated individuals who then might be able to be used for case control study that could be completed more rapidly than the kinds of things that you are involved in now?

DR. WEADON: While we are deciding on someone else to respond to this, I want to come back, I will answer that question, but I also want to address an issue that was raised just a little bit earlier.

And that is that we are no further along than we were two years ago at the time of licensure. I think we need to remember that as Dr. Francoise Meurice, and Dr. Bernard Hoet have shown, our overall control safety data base has doubled from the time of licensure.

So we've added -- we've had a doubling of that control safety data base. Additionally, as

you've heard from Dr. Platt, we've enrolled in the phase IV study, albeit not at the rate we would like to see, some 2,000 enrollees, actually 3,000, we don't have all the data for that additional.

We've heard from the post-marketing adverse experience data base that that, given the considerations outlined by Dr. Ball, is one that is aggressively and continually reviewed.

So it is not that we have not progressed from where we were two years ago, we have progressed. And the questions have been asked, over and over again, and the answers have, to date, been consistently the same.

That the adverse event profile that we saw pre-licensure, have been corroborated in all of the various domains in which we've asked the question.

However, the effort has not stopped. We will continue to look very carefully at how we can enhance the accrual into the phase IV study. We have not, to my knowledge, looked at a patient registry situation. And my colleagues here are shaking their heads, that that is not something that we have considered to date.

So that is not something we have discussed with the agency at this time.

CHAIR DAUM: Thank you. I think that you are hitting on an important issue that the committee is shortly going to be asked to address. And that is that in their view, the committee's view, do they feel that the safety profile at the time of licensure, and the safety profile now, have changed in a way that should concern us.

And has it, or hasn't it, or do we know? And I think those are the kinds of data or opinions, at least, that the FDA would like to hear from us about. And there will be a couple more things that I will charge you with shortly to comment on.

But I would like to hear from Dr. Stephens, then Dr. Luft and Dr. Manley.

DR. STEPHENS: I would like to follow up on a point that Dr. Ferrieri raised a minute ago about basic mechanism of this vaccine, which I still don't understand.

Can you clarify, can the manufacturer clarify the issue of how you think this vaccine works? The data suggests that it neutralizes OspA in the tick as the basic mechanism. But I have trouble with that particular, that that is the only mechanism.

And secondly an issue we raised this morning about the lipo protein component of this

vaccine, what is the lipid, can you clarify that, are there any evidence that antilippid antibodies, cartiolithen, for example, are produced in response to this vaccine?

PARTICIPANT: To answer your second question we have no evidence of that, indeed, we don't know that.

DR. STEPHENS: I'm sorry?

PARTICIPANT: To answer your second question we don't know that.

To answer your first question you mentioned --

DR. STEPHENS: I'm sorry, you haven't looked at the lippid that is contained in this vaccine?

PARTICIPANT: If we have looked in the lippid, at the lippid?

DR. STEPHENS: What is the lippid portion of the protein.

PARTICIPANT: Those are palmodic acid at the interminus of the protein through its natural processing. This is a mechanism that is very common through, in many bacterial proteins. This is during the process.

DR. STEPHENS: What is the lippid

component of the vaccine, structural?

PARTICIPANT: Structurally those are palmodic acids, three palmodic acids at the end of it.

DR. STEPHENS: And the e coli vector puts those on in the same way that borrelia does?

PARTICIPANT: Yes. This post-transitional modification is something that is common to many bacteria.

DR. STEPHENS: I appreciate that, but there is a lot of difference in how bacteria may attach certain fatty acids to their proteins.

PARTICIPANT: I agree. We have checked, and the profile, the lippid profile of the protein producing e coli is similar to the one observed in the protein produced by borrelia.

DR. STEPHENS: So the lipid portion of the protein is the same as that produced by borrelia?

PARTICIPANT: Yes.

DR. STEPHENS: Now, the follow-up question has to do with any evidence of antilippid antibodies produced by the vaccine.

PARTICIPANT: We will look at that.

CHAIR DAUM: You've not looked at that?

PARTICIPANT: No. The first question you asked was about the mechanism --

DR. STEPHENS: The expert, presumably the tick, the OspA in -- and that data, I think, goes back to the '92 study looking at immunofluorescent data in ticks with or without the vaccine.

Is there any other follow-up data to talk about how this vaccine works?

PARTICIPANT: Well, all the more recent data still confirm that the mechanism, as it was described at that point, and you have to take into account two aspects. The first is that OspA is expressed when borrelia is in the midgut of the tick, that is one.

And so when the tick ingests some blood, or some serum containing anti-OspA antibodies, it could be killed, borrelia would be killed within the tick midgut.

This is one point. Now, all the clinical experiments that have been conducted since then, using direct challenge experiments, show that you will clean the ticks from their borrelia infection when they feed on animals that have been immunized with OspA. Does this answer --

CHAIR DAUM: I think so. We are going to move on. There is three more people lined up on the question list, and then I'm going to begin the process

of eliciting some summation comments from the committee., based on this discussion.

Dr. Luft you are next, then Dr. Manley and Dr. Diaz.

DR. LUFT: I just wanted to comment about the lippidation. That the actual lipoprotein, the fact that it is lippidated does almost act as a mitogen, and it gives a whole host of other -- so, I mean, that is --

In a way I feel like I'm almost in a twilight zone when we are talking about surveillance and these adverse events, and I forgot the name of the -- one of the vice presidents from Smith Kline.

What disturbs me is that in the SmithKline presentation there were 950 adverse events. There was a nice presentation of that. And this afternoon we heard testimony from 20 individuals of 20, of approximately 20 people who had very significant adverse events.

And the disconnect for me is I'm hearing that, and I'm seeing that data, and I don't see any reflection of one to the other as if we were in two different universes.

I'm not ascribing what the validity is to these complaints. Certainly I was moved by it. But

the fact of the matter that it didn't even enter into the discussion, or into the charts, or the tables, is disturbing.

And there is some problem in the actual, the adequacy of the surveillance that is currently going on, in that we are not seeing that data in the company's presentation.

And it goes back to my original point about the ICD codes. I think in this particular situation, where you may have an Amazon.com, you have to be able to get assurances, you have to be able to feel secure, you have to make sure that actually there is a very active surveillance system that is going to out, that is going out and actually pulling in these types of cases.

And I think that that is something that we have to consider. I don't think the idea of a passive type of system, or a system that is going to take three to five years to kind of figure out whether we had an adequate power, or whether we had an adequate input of the right information, or whether we were -- whether we cast a wide enough net will really be adequate.

And I invite the sponsors to give me some insight as to why there seems to be this discrepancy.

But, in a way, I think I'm just restating the obvious. This is -- I mean, I can't --

DR. MANLEY: That is my concern, specifically, so if I can speak now, because it is the same question.

CHAIR DAUM: Why don't you, and then we will get an answer for both questions from the sponsor.

DR. MANLEY: I echo that concern, and had a couple of questions which, I guess, this could help us.

How can the manufacturer, or is it the FDA assure the committee that we know what the physicians are doing, and saying to patients, and what kind of information patients are getting before they agree, because since it is not an active surveillance system, how can we be assured, with some degree of comfort, that patients know what some of the side effects, or some of the things that are being reported about the vaccine, before they get it?

And that is really tied to the other question about how can we assure that we have better more active surveillance now that the vaccine has been approved.

CHAIR DAUM: We will ask for a bicameral

response. We will hear from the sponsor, and then I think we should hear form the FDA about this, also.

DR. WHEADON: First of all let me say that we, as a manufacturer of pharmaceutical products and vaccines, take any report of an adverse event on any of our products, seriously.

And certainly the things that we heard today we take seriously. That is notwithstanding we have to also understand that the way the post-marketing reports surveillance system works in this country, not just for LYMErix, but for all vaccines, for all drugs, you do not in how these things are collected capture the emotion that we heard here today.

I'm not saying that that is belittling, or minimizing what we heard. But the way the system is you take the sort of emotion and the gestalt, and the stories that we heard, and you have to then transfer that into event terms like arthritis, like arthrosis, like congenital deformities in the case of whatever.

It all goes into a data base where you do your analysis as objective, and as scientific, and in as rigorous a fashion as possible, to discern whether or not there is, indeed, a signal.

And that is something that you've heard

Dr. Ball talking about, that is something you heard Dr. Hoet talk about, and that is something that we do on a daily basis.

So the fact that what we present on the screen did not carry the same weight, emotionally, as what you heard today, I can't give you a better explanation than what I've just given you.

But I can assure that any and every report that we are made aware of is captured and included in the analysis that we presented to you today.

CHAIR DAUM: Does anyone from the agency want to comment on these two questions? Dr. Ellenberg, Dr. Ball?

DR. KEITEL: Yes, I just want to make a specific comment. One of the difficulties we have with VAERS is we often get incomplete information. So one of the specific reasons we are doing a follow up survey focused on reports of joint problems, is to get complete information, both from patients and from their medical records, in the hope of capturing more of the information about exactly the course of the adverse events that are being reported.

DR. MANLEY: My question really related to before the adverse events. I am still concerned about what level of information is transmitted to patients,

and how can we be assured that they are getting the information they need prior to the immunization?

And can anyone answer that question?

DR. MIDTHUN: THere are a number of different things that we can do. I mean, we obviously start with having the package insert or the label. And I think we've heard a lot of discussion today about things in the label that could likely be better addressed.

And we have communicated with the sponsor, and asked them to address certain issues that have arisen since licensure, and as they indicated, they are working on that, and we are awaiting their response shortly, because obviously this is a very important issue.

I think that the label, itself, is primarily designed for physicians. There is a section in the precaution that says patient information. But it is more information that the physician is given to relay to the patient.

And I think that one of the things that we can consider are other avenues such as patient package inserts, or med guides, or other sorts of things to get information directly to the patient.

And I think that, you know, we invite

comment on that in the discussion.

CHAIR DAUM: Over and above the package insert maybe Dr. Snider might comment, the CDC and the American Academy of Pediatrics have developed little lay language information sheets for vaccines. I have no idea, does such a thing exist for the lyme vaccine, and is it routinely deployed and available?

DR. SNIDER: There is a vaccine information sheet prepared for most of the childhood vaccines. I'm not aware of a vaccine information sheet that is used for lyme. Is there one?

DR. MIDTHUN: I think there is one.

DR. MIDTHUN: I didn't see one in our package.

DR. ELKINS: At the time of licensure we were asked to comment on a CDC draft of one, and did so, and it was my understanding that it was proceeding through the vaccine program office. But I confess I'm not quite sure of its ultimate fate.

CHAIR DAUM: Well, I think the committee is going to suggest that the word go out that we think that should be prepared quickly, and deployed fairly aggressively to people who are about to be immunized.

DR. FERRIERI: I must say that in my experience it is uncommon for physicians to read

package inserts of drugs, or vaccines, and they are depending on what their nurses may say and read.

But I would never rely on a patient hearing from a physician who has read the package insert, and all the details. You can get all this information off websites, and it is voluminous data, and at submicroscopic level of reading it isn't easy to get through all of it.

You have to be very, very motivated to do that, in my opinion.

DR. MANLEY: I agree, and that is the basis of my comment. That this is intended for the physician and not the patient. And if a patient has to sign that they have read the material prior to receiving the vaccine, you have a completely different situation in your hands.

CHAIR DAUM: At least in part. Dr. Diaz, you have been patient.

DR. DIAZ: Well, likewise I would just second that a vaccine information statement could be very useful in a setting like this, for patients.

I had two comments. One was something that Dr. Goldberg brought up that actually I was -- when I commented on this, the plan case control study that I was wondering, also, I know there are many

states that are developing vaccine registries, and I think Maine is one in particular, and I don't know about the rest of the East Coast, and at what level they have done so, nor whether adult vaccination is really entered into that.

But I bring that up as a potential if such exists that one might be able to, very quickly, identify larger numbers of individuals who have been vaccinated, and perhaps add them, or work with them in a differently, perhaps, study.

The one comment that I wanted to make that I guess is really disconcerting to me, in a sense, is that we don't really have any background population base data, that I'm aware of, regarding some of the findings that are being reported by individuals in association with this vaccine, and how they occur in populations regardless of vaccination, ie, rheumatoid arthritis, or transverse myelitis.

I recognize the difficulty with some of these diagnosis, and arthritis, as an example, putting all arthritis together, is -- which may be multi-factorial, could be a problem.

And yet it is still very disconcerting to me that the only thing, the closest I think I came to seeing anything suggestive of knowledge of the general

population was when someone made the comment we would expect to see more women than men reporting rheumatoid arthritis, and that was the closest we came.

I don't know if the data exists, or how poor the data perhaps is. But, additionally, not having that information, and not having that information age stratified makes trying to sort this out really difficult.

DR. BALL: We have tried to look at background incidents for the arthritic conditions. And, as you are suggesting, there is not much data, only really for rheumatoid arthritis is there some population base data, and even that is fairly limited.

And as you've also just alluded to, we have the additional problem of not knowing the age and gender distribution of vaccine recipients, which both of those factors influenced the incidence of rheumatoid arthritis.

And then there is a number of other limitations in trying to apply that to sort of observe versus expected analysis of the reports that we receive.

DR. DIAZ: And I agree, and I kind of expected that answer, and I guess when we talk about things that might be done, it seems so many times we

are sitting here, or other places, with the same kinds of questions, you know, how much of this is occurring in the general population, vaccinated our unvaccinated.

And if there was any way to quickly try and identify that information in some form or manner, again, I realize it won't be pure, but that might be very helpful in the long run.

CHAIR DAUM: Thank you, Dr. Diaz. I would like to -- did you want to make one last comment?

DR. O'FALLEN: Well, pertaining to this issue we certainly have the age and sex distribution of the over 10,000 subjects who participated in the pivotal study.

And I asked exactly this question this morning, what was the expected numbers, and obviously they didn't know. And clearly the rates for rheumatoid arthritis are available for several different kinds of populations, and that could easily have been assessed.

And pertaining to the disconnect, a number of the people that we heard from today said they participated in that clinical trial, and the adverse effects that they reported were never allowed to be reported in that clinical trial.

We had a very small subset of those people in which adverse events were systematically sought out. That has been very disturbing to me throughout the entire discussion.

CHAIR DAUM: Thank you very much. I want to take Dr. Estes question, and then I'm going to pose some scenarios for the committee, and ask for some comment from each member. Dr. Estes.

DR. ESTES: Well, I think this is a vaccine that is used in some very specific areas, and we've heard comments today from people who feel they've had an adverse event from taking the vaccine.

What we haven't heard, and maybe this is not something that is normally done. But there must be data on practices, or specific physicians who use this vaccine.

And this question came up because I recognized a physician in the audience who recognized some complications with a previous vaccine. And that physician, themselves, actually brought this forward and it turned out to be a real event.

Are there physician comments, are there physicians that are very happy in routinely giving this vaccine, and they just don't see a complication with it? Are some of these complications when we have

a new physician in a new area, perhaps a patient that goes to the physician and for the first time asks them to give the vaccine.

Are some of these events occurring in those isolated areas where there might be another reason of why there is a problem?

CHAIR DAUM: Well, I'm a pediatrician living in a pretty lyme-free area. So maybe I will ask Dr. Datwyler to comment on this.

DR. DATTWYLER: Well, one of the things that strike me, and I will answer indirectly, is that what we are talking about we didn't see it in the 10,000 initial study. A big problem.

But if something is fairly uncommon it would slip through. And the highest incidence of this disease is from Rhode Island to Maryland. And that is not what is being looked at.

And I think that there are many physicians in those regions that have probably given a lot of vaccine, and that is probably where the bulk, that is where the bulk of the disease is, that is where the bulk of the patients who receive the vaccine is.

Why don't we encourage a large active study to get to these -- get enough power to answer the question that really needs to be answered, is

there a problem, is there a low event but a bad thing happening out there that we have to know about.

And none of the data, to this point, tells us that. And I totally agree with you that there are, probably, physicians who have vaccinated hundreds of people in these endemic areas, and shouldn't they be the ones that are the targets of a very active study, and you can figure out, in their practices, if you can match them with the vaccinated population, and get on with the study and do it.

CHAIR DAUM: Thank you, Dr. Datwyler.

DR. SNIDER: Dr. Daum, could I clarify the issue about the vaccine information sheet?

CHAIR DAUM: Certainly.

DR. SNIDER: We went out and checked on it. For people who are not familiar, there are vaccine information sheets that are required to be developed in relationship to the vaccine compensation program. And so those vaccine information sheets are official, and are really required that physicians use them.

But there is a vaccine information sheet that has been developed for LYMErix. And even though it is not an official one, there is one available. And perhaps it needs to be more widely used.

I don't have any information about how widely promoted and used it is, but one does exist.

CHAIR DAUM: You may hear, in the comments, as we go around, that people would like it put out pretty aggressively by CDC, and made known that it exists, because it sounds like people didn't necessarily know that it does.

I would like to try to move to another phase of our discussion now, and see if we can do that. And that is to deal with the FDA's discussion issue. And to refresh everybody's memory is to please discuss the safety data and the plans for continued safety evaluation of the lyme disease vaccine.

And I would like to make a couple of focusing comments before we call on members to make their own comments.

And that is that we had, as Dr. Ferrieri articulated beautifully, a safety profile view of this vaccine several years ago at the time our opinion was being sought prior to licensure.

And I think the question, as I understand it, that the FDA would like us to think about, has your view of that view changed? In other words, is the safety profile we are hearing about today, in aggregate, both from the manufacturer, and from the

FDA, and from the reports from people who journeyed here to talk to us, has something changed? And if so, what kind of response should be made toward that change?

In there you heard considerable detail about programs that have been put into effect by FDA, by the sponsor, to continue to gather safety data. In your view, are those adequate? Are there enough things in place to capture the information you believe we need?

Dr. Midthun asks us to also extend this to the package insert, irrespective of your views of who reads it. Do we need to revise it, is it adequate, is it disclosing sufficiently?

WE've heard comments that could be reiterated as we go around the table. There is, obviously, a lot of basic science missing. I don't think it is the sponsor's sole prerogative to provide that basic science, but this committee is well situated to make a statement that we need it.

What do we need? Let's hear it.

And finally, I've heard a couple of calls for active surveillance of vaccine side effects. That is quite an undertaking. And if you really mean it, when it gets to be your turn give us a sense of how

would you do that, and how would you gather data like that, who would pay for it, and how would the data be analyzed and collated.

Other things that people wish to sort of raise and reflect on as we go around are welcomed as well. And to be, variety is the spice of life, so we are going to start today with Dr. Estes and go around to our membership this way. Thank you very much. Dr. Estes.

DR. ESTES: Well, I was not at the Committee meeting when the vaccine was originally licensed, but I think I'm struck by several things.

First I think that Lyme Disease is an important disease. I think it's a disease where a safe vaccine could be very important to our population.

I think that this may be a safe vaccine, but I think my bottom line when I look at everything, and I look at what the recommendations were by the Committee made two years ago, my assessment is that we haven't come too much further past beyond those in terms of answering the questions that the Committee wanted to have answered two years ago.

I personally have some questions about how some of the studies were stratified relative to

previous self-reporting versus Western Blot data.

That's not an area where I'm an expert but I would like expert people to really look at that carefully from some of the original studies.

I found that the studies on the cellular immunity not to be convincing and I think additional studies need to be done.

The studies that were done in the mice did not address, for me, any issues relative to whether this vaccine does or does not exacerbate infection with lyme disease.

I think the pregnancy registry was a start but it's certainly not complete and I didn't come to any conclusions with regards to that. I think the VAERS data is very important but we certainly heard all of the limitations of that data.

I think the follow-up studies there are extremely important and need to be done. I'm concerned about the Phase IV Study. I think everybody's heard really the specific concerns about what -- where we get the data.

I don't think it's coming fast enough and I think other studies really need to be designed to look at the safety of the vaccine.

CHAIR DAUM: Thank you very much. We're

off to a good start. That was very well articulated. Ms. Fisher, please.

MS FISHER: Well, as the consumer member of the Committee, I want to thank the members of the public for coming here and telling what happened to them and to someone they loved after being vaccinated.

I know how hard it is to do that in this kind of forum and if I had been in the audience I would have applauded too to give you moral support.

Last night as I was reviewing the information we were given on Lyme Disease and Lyme vaccine, it became more apparent as I kept going through it, that it was a different disease, different vaccine, same story.

The reluctance, or the willingness of industry and doctors to write off adverse events following vaccination as coincidental, is widespread, and it absolutely impacts on the vaccine adverse event reporting to -- to VAERS.

At the National Vaccine Information Center after 19 years of receiving vaccine adverse event reports, the number one high risk factor that we have identified, is doctor's continuing to vaccinate in the face of clear adverse event symptoms.

And some children are literally vaccinated

until they die or are brain damaged because doctors are unwilling to recognize that an event is -- is connected to the vaccine.

The second high risk category is vaccinated with the coinciding viral or bacterial infection. And the third is vaccinated individuals who have a strong family history of autoimmune disease, particularly Rheumatoid Arthritis, thyroid disease and other kinds of autoimmune disorders.

And I found it very interesting that there has been an identification, a potential identification, of a genetic factor, with regard to this vaccine.

I support better labelling by the manufacturer what is known now regarding reported adverse events and also the moving of some of these from a precaution to a contraindication, particularly with regard to vaccinating individuals who had -- have had previous Lyme Disease or have had symptoms of Arthritis, etc. after vaccination.

And, certainly basic science research, FDA-driven basic science research, particularly into antigenetic predisposition to adverse response to vaccination and then, of course, active surveillance of the vaccine adverse events that are being reported

around the country.

CHAIR DAUM: Is your view that the basics, that the safety profile of the vaccine has changed, though, since we heard it two years ago, or is this an ongoing concern of yours about the same?

I need a sense of -- that what you're feeling is about the change.

MS. FISHER: Well, since I was not on this Committee when the decision was made all I can say is that looking at what little I know about what the Committee looked at then, this appears to be a continuing problem that -- that is simply magnified now over -- over time, and that it cannot be dismissed.

We cannot continue to dismiss these as coincidental events, when we continue to have the patterns, and they are clear patterns, and I found -- the reason I made the statement I did is that I found that this -- this is the same with regard to other patterns that have been seen after vaccination.

And, of course, a really good lesson that we learned was with DPT Vaccine. Those patterns were found to be correct because now we are seeing far fewer reactions to DTAP than we did to DPT.

And so that experience, that anecdotal

evidence that was presented, has been shown to be correct with the lessening of the symptoms after DTAP.

CHAIR DAUM: Okay. Thank you for clarifying. Dr. Diaz.

DR. DIAZ: Dr. Estes covered at lot of the comments that I was going to make actually.

I, likewise, was not here initially and yet, based on the materials that have been provided to me, and the information set forth, based on the studies and analyses done so far to date in my mind the safety profile of this vaccine hasn't changed significantly in terms of the data from when it was presented for licensure.

That having been said, perhaps that's -- I also tend to agree that there's not enough data, though, to say that it won't change in -- like this Phase IV Studies that are currently being done I don't feel that, based on the enrollment, that there is enough data there to -- to really make a statement along those lines from the standpoint of -- of the safety.

So I'm actually sitting in a position where I -- almost doesn't matter whether I was here two years ago or here today, I feel like the information is fairly comparable, in a sense.

And, yet, some of the extra data that's been presented -- like the mouse model data, I didn't think was really -- answered any of the questions about autoimmunity in particular.

And I'm not sure that projected studies will necessarily answer all of the questions that have been raised, likewise.

I would be very much in support of further educating the public, certainly, and physicians regarding information about the vaccine; who should be vaccinated and who should be considered for vaccination.

Likewise, I would encourage the FDA to work very hard with the sponsor to address some of the concerns, perhaps such as HLA typing, prior vaccination, etc. and work out some way to -- to at least inform people of those concerns, albeit them not proven at this point in time.

And finally, I again raise my concerns over the enrollment issues with the studies and it's disconcerting that we -- certainly not from any lack of effort, obviously, on the sponsor's part to do so. It's just that the numbers aren't there and yet the numbers do probably exist out there somewhere.

And I would herald what was commented upon

that there probably are many, many physicians who have given hundreds of doses of this vaccine.

And if a study were designed, one could perhaps answer the question a little bit faster than what is currently projected. Albeit, again, I guess I have to say that I don't know how many more people will actually come into the database once the Minnesota and the other groups are enrolled. So I would temper that by looking at those projections.

CHAIR DAUM: Thank you. Before I call on Dr. Manley, I guess just to clarify one thing.

I don't think people needed to be physically present here to compare the database that was available at licensure with where we are today.

Some of the same data were presented this morning and the information has been available. So I would like to hear people's comments as to whether they think it's basically a question of whether there's new concerns or whether they think that we're still -- we have concerns and we still have concerns but -- and we'd like them answered more quickly.

It's a slightly different spin on the same issue.

DR. DIAZ: Right. I might clarify, because obviously, you interpreted what I said,

perhaps in a different light. My comment in saying that I wasn't here before and yet, am here today, was not to put forth any concerns about being able to look at the data from that time to now.

It was the issue that there's not very much new data.

CHAIR DAUM: Thank you. Doctor Manley, please.

DR. MANLEY: Well, I essentially concur with what the two previous speakers have said that the concerns that were expressed two years ago seem to be the same concerns that we have today.

And, even though the sponsor said we know a lot more, we have not really resolved some of the issues that were before this Committee then.

I, too, am concerned about the slow enrollment and it seems that at the rate we're going, it's going to take us a long time to answer the questions that, are frankly, quite troubling, I think certainly to me, and I'm sure to others.

And there are some things that are more troubling than others, certainly the pregnancy registry and almost the lack of almost no information in that area that we can really relate to right now.

Certainly pediatric age group and the

question that came up near the end of this discussion and that is what patients know and when do they know it, and how much assurance we have that physicians are communicating with patients about quotes even if they are not proven, some of the adverse reactions that have been reported.

It seems to me that that is very troubling and that whatever we direct FDA and the sponsor to do, going forward, that that has to be addressed and that the surveillance should be much more active than it is currently being described to us.

And that short of being able to address these issues, one has to really look at the cost benefit ratio again.

You know, it's been said many times and outlined very clearly. This is geographic, age distribution, treatable with antibiotic and I think that ultimately this question has to be addressed again by this Commission.

CHAIR DAUM: Thank you, Dr. Manley. Dr. Midthun did you want to make a comment?

DR. MIDTHUN: Yes I would. I think as people go around and perhaps some obviously -- there's been the issue of a higher, the linkage shall we say an association between DR4 and the treatment-resistant

Lyme Arthritis and, therefore, concerns whether perhaps a certain HLA type might put you at increased risk for something for vaccine -- for vaccination adverse events related to vaccination.

I guess I would like to just go back though to the efficacy study and visit the issue that likely roughly 30 percent of the individuals enrolled in that study were DR4 positive just based on what we know of the prevalence of that.

And that we, in that particular study, did not see a difference in the rates of Arthritis or Arthrosis or other things. So perhaps if people might as they go around if they want to address that particular issue and how that might be explored further, given that backdrop, that would be very helpful.

CHAIR DAUM: Thank you and we'll go to Dr. Griffin.

DR. GRIFFIN: Okay. I also was not here two years ago, but I have looked at the data and it seems like that we have more data but what we have is more of the same data. And that what we don't have is any new insights or more in depth examination of the kinds of questions that were raised at that time.

As I think I've already indicated, I don't

think the animal model is, contributes much, but it sounds like some other people have animal models, that might actually be useful in trying to sort out some of these issues.

And I think that really needs to be some basic, more basic science approach to a better understanding of the immune response to this vaccine of the types of immunologic abnormalities or whatever may be ongoing, and people who have complications.

And I'm sure that a lot of that kind of information is available for Lyme Arthritis but also for various complications of Lyme Disease.

But that the opportunities are available for really doing some excellent work and we get hints, I guess is most frustrating to me, is there would be hints that actually studies have been done, the data didn't show much, but we weren't allowed to see that data so there was no way that I can independently say I don't -- you know -- I think that that shows that, you know, it's very reassuring or whatever.

So, I was frustrated by that lack of sharing with us, I guess, the data that does exist, particularly for cellular immune responses to OspA, the relationship of that to HLA, and types.

And I think that would be the kind of data

I'd be asking for, would be a better understanding if those people do respond differently than the people that have a different HLA type.

They may not be important but we can probably figure that out. But those kinds of studies ought to be done and they ought to be shared.

I certainly agree with the need to get active, some sort of surveillance that answers the question that basically, I think, Dr. Luft said most directly: Is there a problem or isn't there?

And, right now, I don't think any of us feel comfortable in saying there's not a problem or uncomfortable in saying there definitely is a problem. We just really don't have the data on which to be able to make that judgment.

So those are the things that I would suggest.

CHAIR DAUM: Thank you very much Dr. Griffin. Let's move on to Dr. Kim, please.

DR. KIM: Well, I also agree that we still have similar safety concerns remaining with us compared to two years ago. Again I did not perceive any improved understanding or knowledge on those issues whether I feel more safer now than two years ago.

I think is the same concerns are currently under investigation and ongoing. But I think it requires continued investigations to address the issues that have been with us for the last two years.

And the second issue, again, along the lines, again everybody, the previous speakers have indicated issues regarding HLA DR and OspA interactions.

I think that certainly needs to be addressed soon in a format that is scientifically of acceptable fashion and at the same token we have seen many vaccines have changed the format over the years.

So if, indeed, you know again, we all agree that this is important this is, therefore, vaccine is needed, then I consider the current vaccine as, perhaps, first generation.

Then I think that we need to look into, a perhaps, second-generation vaccine which, if that is possible, then perhaps, eliminating the cross-reacting epitopes, apparently that -- those regions do not overlap with the protective epitopes.

I'm sure that those kinds of constructs can be serum proteins and purified proteins can be constructed and I don't know whether they would be functional or not, but if indeed they are then I think

some of the issues then need to be considered for developing safer vaccines for Lyme Disease.

And then, third issue, is I also support that some sort of a vaccine package needs to be developed to indicate or to at least to share the concerns that have been presented to us today with the consumers and physicians.

I think they need to know what is going on, you know, whether this is real or not, you know, there was a meeting to address these issues. I think they need to know that.

And then, lastly, there is a study going on in pediatric population I'm very concerned about that despite, you know, having all the issues discussed today and I soon like to see a very close monitoring of a pediatric studies for the safety and other issues that have been brought to our attention today.

CHAIR DAUM: Okay. Thank you very much, Dr. Kim. Dr. Stephens, you're up.

DR. STEPHENS: I think the comparative safety data that's been presented really hasn't changed, in my opinion, from what we saw from the '98 review.

I wasn't on the Committee at that time,

but certainly, the data provided doesn't suggest that there's been a significant change. What has changed in my mind is the weight of what is largely anecdotal data, but certainly a huge body of anecdotal data suggesting that there may be, that we may be missing something with this vaccine.

I think that's the concern of -- of many of the Committee members. I'm bothered by the issue of this vaccine in the setting of prior Lyme Disease and I'm also bothered by the issue of this vaccine with certain HLA types.

And I don't think we know a lot about the immune response to Borrelia in general or specifically to this vaccine.

I would certainly, a point made about active surveillance in endemic areas is something that I think should be strongly considered as well as increased patient information and potential increasing warnings regarding the package, package insert.

CHAIR DAUM: Thank you very kindly, Dr. Stephens. Dr. Snider.

DR. SNIDER: Well I was here. I remember, and I think there is one thing that's different about the atmosphere and that is that the characterization of Lyme Disease was different at that meeting, and

that there were a number of people from the general public who made comments about how devastating Lyme Disease had been.

And I do recall very vividly subsequently when the Advisory Committee on Immunization Practices released its statement about Lyme Disease should be considered for people in certain high risk areas with certain high risk activities, that in that we made some comment, which seems rather benign, to the affect that most cases are treatable with antibiotics, that we received thousands of letters from the public indicating that that wasn't true.

And, that there were a lot of treatment failures and we weren't being as supportive of the vaccine as we should.

And so I just remind people of that particular environment, and that information that people delivered.

With regard to the concerns, I guess since some of my quotations were in the written document it's clear that I had concerns at that time about long-term affects.

I think we do have some more data, and I appreciate the sponsors obtaining that additional data for us. Unfortunately, as in many cases with many

vaccines, when we're talking about uncommon events, if not rare events, we don't have enough data to be able to draw any definitive conclusions.

And so I would agree with a lot of my colleagues here that the concerns that we had back then have not been completely alleviated, and in fact, additional studies that had been done in the interim have raised our concern.

And we certainly are concerned about what has happened to the people who spoke here, and their family members, and have a great deal of concern about whether that is related to the vaccine or not.

As Dr. Estes pointed out, you know, a number of studies could be done from the standpoint of animal studies, in vitro immunologic studies, clinical studies, and so forth.

But I think we have to choose very carefully because there aren't unlimited resources.

I do think the post-marketing cohort study was an excellent idea as I think everybody else is very disappointed, and I'm sure the sponsors disappointed as well, with regard to the enrollment of persons into that study and the fact that we don't have more information now.

I do have concerns when we talk about

doing active surveillance, although on the surface it sounds like it might be -- help pick up more cases, it would have to be done in a way that doesn't bias the study as Dr. Platt alluded to.

Because if everybody knows that you're looking for certain conditions that might result from LYMErix, then that's what they'll give you.

And, therefore, you would have to do a very carefully designed study in a manner that I haven't thought of exactly right now. That's not to say it's impossible, but to more aggressively go after cases and invoke vaccinees and controls.

The registry idea is something that I wouldn't totally give up on. I think it's worth exploring. I realize that all of these things would be quite costly and logistically difficult and may not get us down the road any more rapidly than what -- the speed we're going with regard to the post-marketing cohort study that's already been designed.

I am very concerned about the potential long-term effects, and one of the things we haven't talked about is, you know, how long will efficacy remain in future years, are there going to have be additional boosters?

And if there have to be additional

boosters will that present additional problems. So I think the problems with this vaccine are going to continue to be in front of us, or at least the potential problems.

I agree with folks who indicated that there need to be some modifications in the package insert and that we should more aggressively promote a vaccine information sheet that has the appropriate information.

I apologize I didn't look at the package insert but it sounded to me from what Sid Wolfe said that in the indications area perhaps need to be modified to reflect the geographic risk as well as the activities risk.

I think the manufacturer already has indicated a desire to put in something about hypersensitivity reactions.

And then there is the issue of what to say about the possibility of chronic arthritides or other autoimmune diseases. And I don't think we have definitive information that indicates that those are long-term adverse events.

On the other hand we do have some plausible hypotheses that have not been disproven and so it's not clear to me in this kind of a setting how

one deals with that in a vaccine information sheet or in a package insert in a way that is understood by the average practitioner or the average patient.

CHAIR DAUM: Thank you very much Dixie. I'm going to do a little bit a reverse field here because there are some -- we're starting to encroach on airplane schedules, assuming that planes are running on time.

And, we'll actually start at this end of the table with Dr. Ferrieri and work our way up, if that's okay. And, we are aiming for a 5:30 adjournment. So, please be succinct, if some things already been said in some detail, you can merely say that you agree with it.

But please feel free to expand on points, should you wish to. Dr. Ferrieri

DR. FERRIERI: Well, I was here the last time on this subject, also. Dear BBC, New York Times, London Times and CNN and everyone else, please don't call my office.

I don't return any calls on Lyme vaccine. What I say is part of the public record. It will be posted on FDA's website. Sorry if that seems intractable but I feel that we can only be misquoted on what we say.

I had my chance to say several things at the beginning today, so I won't reiterate them. I feel that there is more data to examine, but the concerns that I had personally before have not been assuaged by anything I've heard today. And I feel the background noise that we're hearing may be greater.

My concern is greater than it was before and there are several areas that we have not yet been able to gain information on that I commented on before and that Dr. Snider has resurrected, the issue of further boosters, the length of protection, etc.

In a nutshell, I think FDA has to grapple with the serious issue of is it sufficient to do revisions to the package insert. Well, that really -- how far will you be pushed to have to do something more drastic than that, Dr. Zoon and Dr. Midthun, et al?

I think that you have to deal with what you have in front of you. Are we going to be able to resolve these issues expeditiously or should you put a moratorium on the vaccine until you are able to very critically examine what we have and what is realistic to move forward.

It's with great regret that I say this to you. I've never had to say this before. I've never

heard, in all of the years I've been on the Committee heard this type of concern iterated without Agency response that has satisfied the dissatisfying from my point of view.

I consider what we're dealing with today to be very, very serious and I would like to throw back to you the need for you all to reexamine how this fits in to your mission and in the public health realm.

And, so, I agree with others who would like more basic science work done as I iterated in the beginning. The Phase IV Study dissatisfaction may not, perhaps it will come forward sooner -- maybe not.

There are too many ifs here for us to feel secure that the answers will be forthcoming.

So, again with great regret, I think that you have to examine where you are and what we owe to the public.

CHAIR DAUM: Thank you, Dr. Ferrieri. Dr. Myers, please.

DR. MYERS: Well, I think we do have more data. I wasn't here. And, it's reassuring, but it's very limited. It's a cross-over design functionally.

I think it's important to say that at this point there is no evidence of chronic arthritides

being associated with the vaccine.

That said, though, I think everybody's expressing the same concern that such an association could exist, it has biologic plausibility. I've heard a couple of people comment that they suspect that the possibility of a VAERS signal, and that this needs to be aggressively pursued.

I think the concern that I have is that we need the data as quickly as we can possibly get it from as many sources as possible to allow the assessment of likelihood of causation versus coincidence.

I just don't think we have that. I think vaccine information, providing vaccine information, is -- it would be very important.

But I think the real issue that I would like is to see an aggressive approach to getting the data to allow an assessment. I think the Cohort Study is really important. It's going slowly. It's going to be an important study and I think it's important not to dilute it or allow it to collect data that isn't accessible across the whole study

With that said, there are an enormous number of vaccinees that aren't being collected that are in areas where the attack rate for Lyme Disease is

much higher than Massachusetts.

Rhode Island, I guess, is going to be part of the Cohort Study. But, there's Connecticut. There's Long Island. There's all the way down through the mid-Atlantic States.

And I think it's really critical that we try and get that data as quickly as possible so that we can do the assessment that needs to be done and either say that this is a problem or we can allay the concerns about it. I guess that's it.

CHAIR DAUM: Thank you very much, Marty. Dr. Goldberg.

DR. GOLDBERG: I was not here two years ago, and I must admit, as I reviewed the materials, that I might have had difficulty approving the vaccine at the time -- voting for approval at the time.

I don't see sufficient new data. And it makes me very nervous that the rate of accrual of new data is too slow. And so, what I would urge, is that with all speed, you start to do some surveillance. Whether it's active surveillance, registries in combination with the ongoing efforts.

Because I think you have to cover the bases on a lot more fronts than you are and much more aggressively if you want to get some

resolution.

I do believe that patient information has to be made much more accessible. One possibility is that that all done, that all provided, the rates of vaccination will decrease even more and so it will become even harder to definitively collect more data.

And I think you have to weigh all of these, somebody has to be, the FDA and the sponsor have to be working out what the numbers are and what kinds of timetables you have to come up with to get some of these projects underway.

I also was concerned about the discussion of case definition that came up in the open part of the hearing. And, the fact that in the original studies this very specific definition was used and I would urge, that if it's possible, to reanalyze that data with sliding definitions of cases. And determine, what kind of affects misclassification on case definition could have on the efficacy results.

I don't know if that was done. There wasn't enough detail provided. Basically, I think everything else I would say was covered already.

CHAIR DAUM: Thank you very much. Are there any more airplane concerns on the remaining people that need to speak or can we just go in

sequence? Good. Dr. O'Fallen.

DR. O'FALLEN: I too was underawed by the amount of data that were available two years ago regarding adverse affects, and read with a great deal of interest about the Cohort Study that we now hear is in serious jeopardy.

But that was why I was asking so much about it because I thought it would be so essential. I think those data collected in a systematic a way as possible, and I truly do approve of the design of the study that is currently underway and I only wish that they could access more data. I think we do need more data.

There is evidence that something's going on out there, I truly believe, and my answer to the question that was posed so eloquently and so frequently from the floor several times today, is no.

CHAIR DAUM: What question is that?

DR. O'FALLEN: Would I take the vaccine.

CHAIR DAUM: Dr. Davis, please.

DR. DAVIS: Thank you. I have several issues that I certainly concur with our prior speakers regarding. Not in any one particular order.

One question I have would be the impact on what we haven't heard and unfortunately we didn't hear

in a more of an anecdotal way, from one physician, who had provided a letter for us to read.

But what is the impact on the occurrence of Lyme Disease in communities where the vaccine has been more widely used? Are there any decent surveillance data in those communities where we can get at least some assessment of trends in actual occurrence of the disease?

Some of these communities may be actually smaller and I think being able to make an appropriate assessment of data in those communities may be difficult to do. But I think very important.

Along those lines, what Dr. Dattwyler had recommended earlier, doing an objective assessment of physicians experienced with using the vaccine and their experience with side effects, I think would be important.

I certainly concur with that and I'd also want to make sure that the whole issue of their recognition of side effects is important as well, because of the issue that was raised, are people not adequately recognizing what may actually be an event. So I think probing that, of course, would be important to do.

One thing I'd be interested in also, is