

**Plenary Session III: Immunology and Pathogenesis and  
Plenary Session IV: Bio-Ethics  
Fourth MIM Pan-African Malaria Conference:  
Yaounde, Cameroon  
November 16, 2005**

---

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

[START RECORDING]

**ROSE LEKE:** Plenary Session III, where we have the immunology and pathogenesis session. This session is dedicated in memory of Dr. Peter Pearlman [misspelled?]. And before we start, we'll just have Dr. Max Walgreen [misspelled?] say something to us to remember that excellent researcher, Dr. Peter Pearlman. Thank you, Max.

**MAX WALGREEN:** Thank you, Rose. I just want to say a few words for you to remember and for us to remember Peter for a few minutes. When I arrived here at the airport, sitting in the lobby waiting for the passport to be processed, I saw Hviid, but I also saw Peter. As he always came to the meetings in his suede jacket and a red sweater. So [inaudible] which you do with people that you have known for a long time and that you love very much; and Peter was one of these people that you respected and you loved him for his simple ways of being and his brilliant science.

Peter was born in Sudet-Deutschland, in actually, present Czechoslovakia, came due to the Holocaust and the problems to Sweden in the '40s, and started there to become a biologist and moved rapidly to Stockholm from [inaudible]. He worked on sea urchin during the 1950's. And if you would ask Peter today when he was alive, he would have said, "My favorite finding"—you know, he made many important findings. I'll tell

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

you a few about them.

His favorite finding still was to discover that fertilization of the egg is a receptor mediated event. He showed that in the 1950s in a tremendously classical paper in [inaudible] in 1955. That time brought him into immunology. The rest of the days he spent working in immunology different aspects. He discovered the cytotoxic T-cell in 1963, in a not serious colitis system, published in the *Journal of Experimental Medicine*, and then met Hviid. Hviid and Peter worked maybe in some kind of endosymbiosis almost, together, for so many years; lived together, worked together. And Hviid is here today, sort of continuous of the work.

In 1971, Hviid and Peter discovered antibody mediated cytotoxicity, ADCC, another very important discovery when it comes to cellular immunology, and at the same time, developed the first ELISA test ever. So Peter had a tremendous impact on the immunology of the 20<sup>th</sup> century. And when asked by the Rockefeller Foundation if he wanted to have a grant from the [inaudible], he said, yes, and continued his days to work in immunology of falciparum malaria. And Hviid and Peter continued to contribute to the vast field of science which malaria is.

For example, Hviid and Peter showed one of the first antigens in the membrane of the malaria affected red cell,

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

1984, in the *Journal of Experimental Medicine*, 155, which was also [inaudible].

So Peter was a great person, a wonderful individual, that we will miss, but he was also one of the brilliant scientists of the 20<sup>th</sup> century. Thank you so much for honoring Peter with this symposium. Thank you, Rose.

**ROSE LEKE:** Good morning, distinguished colleagues. Could we request a one minute silence in memory of Peter Pearlman? Now, I have the most pleasant duty to introduce briefly the speaker for this plenary session. He is a eminent parasite immunologist, whose contribution to the field can fill many books. But I'll be brief. He says he lives in Copenhagen, but I think he would be better found in any place in Africa and not in Copenhagen.

Lars Hviid started in malaria immunology around 1986. He stretched the length and breath of Africa, and in special areas that he's made contributions is cellular immunology, [inaudible] immunology, and recently, taking up the challenges of the various antigens. Who better then to tell us about acquisition of immunity and what better vaccines we can use to tackle malaria than Lars Hviid. Lars, thank you.

**LARS HVIID, Ph.D., Sc.D.:** Good morning, dear friends and colleagues. I must admit, when I went to bed last night, I thought that about this time tomorrow morning, I would be a

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

very relaxed person. I still am looking forward for this relaxation to set in. If I can have the next slide. Like Groucho Marx, I would like to start by saying that before I start my talk, I have a few important things to say. In fact, I have two important things to say. The first of the things that I want to emphasize is that I will be talking in the next half an hour or so, exclusively about immunity as it is acquired by people who live in areas where they are continuously exposed to parasites. I will not be talking about vaccination-induced immunity. I believe that these two things may not necessarily be the same.

Secondly, illustrated in the second line here, what I will say represents one person's point of view and one point in time. There will be people in the audience who will have other points of view, and as new evidence becomes available, I think that in some future point and time, even I may have a different point of view. But I think that really is in the nature of science.

With those cautionary remarks out of the way, I think the good thing about malaria immunity is that it works. Next slide please.

Over a period of years, people who live in areas of continuous exposure to malaria parasites do develop substantial protection from the disease, first acquiring protection from

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

fatal and severe disease manifestations, followed by protection from uncomplicated disease, and eventually acquiring substantial protection even from asymptomatic parasitemia. Malaria in areas of endemic transmission is thus mainly a disease of childhood.

The bad thing about malaria, of course, as you saw in the previous slide, is that acquisition of protection is a very protractive process, and in this process, many, many children fall victims to the disease and suffer fantastically, and many of them die. Some of them even suffer and die really from the consequences of the immune system's attempt to combat the infection.

But from an immunologist point of view, perhaps the worst thing about malaria, is our fragmented knowledge about the targets. We don't really know how this immunity works, what targets are engaged, and what the mechanisms of this immunity are. Perhaps that is a little bit too bleak a view. And in fact, we have been knowing for close to half a century, as shown in these slides, that what really cuts the cake when it comes to naturally acquired immunity is immunoglobulin, as shown in passive transfer experiments by Cohen and McGregor—could you go back please—by Cohen and McGregor, and since by [inaudible] group in Thailand, that if you give IgG to people with malaria, it leads to a rapid resolution of fever and of

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

parasitemia. Next slide, please.

The question then becomes if we agree that IgG is very important, what are the targets of this IgG? And I can think of at least three main groups of targets that are illustrated in this slide. First, we have the sporozoites, the stage of the parasites that is injected when an infected mosquito takes a [inaudible]. And antibodies to the main antigen of the sporozoites may well interfere with the invasion of the sporozoites in the liver, as has been shown in classical experiments with irradiated sporozoites, and we've got even very encouraging news from the Vaccination Trial in Mozambique yesterday at this meeting.

Another obvious target of antibodies would be merozoites that could either block or interfere with the emation [misspelled?] of these parasites into the red cells they infect, or with subsequent development of parasites inside the red cells; and I have listed some of the candidate antigens being proposed to work in this manner.

Finally, there is a group of antigens that I will call in this talk, variant surface antigens, or abbreviated, VSA, for short. Perhaps, to many people, better known as PfEMP1. There may be more VSAs than PfEMP1, but the PfEMP1 molecules, for sure, are the best known. These molecules are mediating [inaudible] of the mature parasites in various tissues, and are

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

the reason that we only see the early forms or the written forms when we do peripheral blood smear of malaria patients.

I will try to argue in this talk that when it comes to naturally acquired immunity to malaria, these antigens are perhaps the most important ones. And I will base my argument by trying to ask five questions, that are shown in the next slide here, in the course of this talk. I believe that answering these questions becomes very difficult without assuming some variant specific immunity, but perhaps that is a challenge to take up from some of those disagreeing with me.

Before I start answering these questions one by one, I will just introduce, very briefly, to those of you who are not familiar with the variant surface antigens what they are all about. The variant surface antigens, are antigens that are actually produced by the parasites and are exported from inside the parasite through the iridocyte unto the surface of the infected red cell, where they are put into these election [inaudible] structures that cover the surface of the infected parasite structures called knopps [misspelled?], and which mediate the sequestration of infected red cells in various tissues, as shown in the slides.

An important point for you to keep in mind as we go along is that each single parasite, each individual parasite or clone of parasite has the capacity to express many different

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

antigenetically different and functionally different variant surface antigens. For example, the genes that encode the PfEMP1 molecule that I mentioned was a big important VSA family, is encoded by approximately 60 [inaudible] in each single parasite genome.

Next, it is important to keep in mind that the parasite has the capacity to switch the expression of different variant surface antigens, and as such, it can change both its functional and genetic makeup as time goes by. We believe, at least for the moment, that this means that the variant surface antigens expressed by individual parasites are all the same on the [inaudible], so that each of the knobs on an infected erythrocyte will actually be composed of the same variant surface antigens.

How the parasites switch from expression of one variant surface antigen to another is a point that is of great importance and under intense study, and I have put some of the key papers trying to elucidate these mechanisms at the bottom of this slide, as I have put other key papers in various other slides as we go along, where you may be able to find further information about these things. Next slide.

So let me go into trying to answer some of the questions that I have asked myself. First of all, why do only some parasites cause clinical disease? As you probably all

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

know, that if you go into an area of very intense parasite transmission, and go into any primary school, many of the children in that primary school will be harboring asexual parasitemia; in some areas, it may be as many as everybody. And nevertheless, only a small proportion of these children actually show any clinical signs of infection; and that is, to a certain extent, somewhat [inaudible].

I will try to show you some of the experiments that have tried to address why this may be the case. The design of these studies are this kind, longitudinal studies, where groups of children have been followed over time from before they experienced a malaria attack, during the disease or episode, and follow-up during [inaudible].

At the time of the disease, people have then looked at the antigens expressed, the variant surface antigens expressed by the parasite causing the disease episode, and seeing whether the person had antibodies was [inaudible] for this particular variant before and after the disease episode. And invariably, the answer is no, when you use samples obtained prior to the attack, and yes, when you obtain samples after the resolution of the disease episode.

This is perhaps not terribly exciting, and that is probably something you could see with most antigens. It becomes a little bit interesting though if you take another

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

variant surface antigen than the one expressed by the parasite causing the disease episode in this child. And in that case, the VSA—I've called it non-X here, as opposed to the VSA-X causing disease in the child—could you go back one, please. What you will see is that the antibody responses to other variant surface antigens than the one involved in the disease episode, there is really no change in levels of antibodies to such variant surface antigens as time goes by. Next slide, please.

This is just to show you what this looks like in real life. Here we have an individual followed over a period of a year. And you will see that this patient experienced a clinical attack at the time point indicated here by a red arrow. And the antibody level curve shown in red represents the levels of antibodies to the variant surface antigen expressed by the parasite causing the disease episode at this point and time. And you will see that prior to the disease episode, there really were not very many antibodies to speak of. But immediately following the disease episode, there was a rapid increase in antibody levels.

In the graph, I have also shown antibody levels to variant surface antigens expressed by other parasites, and you see that they generally don't change very much or in any symptomatic way as time goes by. They are either uniformly low

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

or uniformly high. And that would lead me to the tempting conclusion that there seems to be some kind of threshold. The higher the level of antibodies indicated here by the degree of [inaudible], the more protected you are; and the individual who got infected by the red parasite, in this case, would also have been susceptible to infection with these parasites that are at the bottom of the graph, but would probably have been resistant to the parasite at the upper part of the graph. Next slide, please.

These kind of ideas have led us to the theory that what really matters is that immunity is acquired in a way as what we could call immunological gap-filling. You have a lot of gaps in your physiological non-immunological defense mechanisms, and most parasites will be able to pass those regardless of which variant surface antigens they express on the surface, and a non-immune individual, this will be the acquired immune defense—could you go back one please—would be equally [inaudible], allowing most parasites to pass through the acquired immunity.

The next slide then show that as immunity is acquired, these holes are then filled by variant specific antibodies. You will note also at the end of the slide here that I have frame here, that if there is a parasite expressing a variant surface antigen that for some reason cannot penetrate the non-

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

immunological physiological barrier, the immune system does not see such a parasite, and, of course, no acquired immunity is developed through this parasite. And the significance of this I will return to in a minute. Next slide, please.

So the second question then is, why is it easier to become immune to severe malaria than it is to become immune to uncomplicated malaria and asymptomatic parasitemia? I think many of us who start thinking about this for the first time would think that it probably should be the other way around. Next slide. And the answer to why it is the case stems from studies such as this one, where the last group of children have been studied and plasma samples collected. And as we can see here, if you then look at antibody levels to variant surface antigens on the surface of the infected red cell, as the age of the plasma donor increases, levels of antibodies become higher. And that goes no matter which parasite you look at. Again, this is perhaps not very exciting, and you could probably make a similar slide for many or even most other malaria antigens.

If you look at this in a slightly different way, however, it starts to become interesting, I think. If you start sorting the parasites according to the age of the patient from whom they were obtained, you will find that parasites obtained from young children are usually easier recognized by antibodies in the plasma of children than parasites obtained

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

from older children. This suggests that as immunity is acquired, somehow, the expression of variant surface antigens is modulated; and this really applies to essentially all plasma samples that you may care to study.

So variant specific antibody recognition does not only increase with your age, but the expression of variant surface antigens also depend on the age of the patient with the parasite. Similarly, if you sort the parasites, not in order of age of the patient, but rather according to the severity of the disease in the patient—here I have shown the most severe parasite to the left part of the slide, and the parasite from the patient least severely ill to the right—again, you will see that parasites obtained from severely ill patients are generally much better recognized by antibodies in plasma than parasites obtained from patients with uncomplicated infection.

I've tried to summarize the whole thing in this slide. And these findings have led us to staff operating with two main groups of variant surface antigens, those that we call VSA-SM, for severe malaria, as opposed to those we call VSA-UM for uncomplicated malaria. And we generally find that parasites expressing VSA of the SM type are more often recognized by antibodies in plasma, and are more often recognized at high levels by antibodies in plasma than parasites expressing the variant surface antigens of the UM type. Next slide.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

So, according to this model, it seems then that as immunity is acquired and this immunological gap-filling takes place, it actually takes place in a defined order, starting with antibodies to the SM type variant surface antigens, and ending with antibodies to the variant surface antigens of the UM type. And if that is really the case, it would explain why immunity to severe malaria is acquired prior to immunity to uncomplicated disease. Next slide, please.

Then, of course, you may ask, why is it that variant surface antigens of the SM type tend to dominate in children without [inaudible], in general, in individuals without any immunity? We believe that that is because variant surface antigens of the SM type are some sort of competitive advantage [inaudible] infect a person without any pre-existing immunity, and that this will leave these parasites to have a greater effective multiplication rate in the body, and they will thus simply outgrow parasites expressing less efficient variant surface antigens.

This idea was first published in a paper from our group, published last year, and is further developed in a paper published this year by Thomas Lawson [misspelled?], where we followed a group of Dutch volunteers who were infected by malaria parasites, non-immune Dutch volunteers, and we could show that as the infection went on, still before development of

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

clinical symptoms, the expression of variant surface antigens in these patients rapidly concentrated upon expression of variant surface antigens of the SM type.

As immunity then is acquired, the competitive advantage of the SM type variant surface antigen gradually goes away, and the infections will tend to be dominated by variant surface antigens of the UM type that will tend to cause uncomplicated disease; and eventually, as you have seen, both the SM expressing parasites and the VSA-UM expressing parasites, you have reached the stage where you can enjoy substantial protection from both severe and from uncomplicated disease. Next slide.

The third question, why is it a problem to become pregnant? There can be a problem, of course, in many respects, but I will restrict myself to talk only about why is this a problem in terms of malaria. It is a problem to become pregnant in terms of malaria as has been shown in many studies and for a long time. This is just one example of the situation, comparing the incidence of parasitemia and the density of parasitemia in pregnant and non-pregnant women. And you will see that the pregnant ones are both more often infected, and those that are infected have higher parasitemias than those that are not pregnant.

That has for a long time been seen as a consequence, an

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

unfortunate consequence, of some sort of unavoidable immunosuppression associated with pregnancy that is necessary to protect the fetus from being rejected by the immune system of the mother. That explanation has one major difficulty, and that is shown in this slide, namely the parity method, if it's true that pregnant women are more susceptible to malaria than other women and men; but if it's also true that this is really only the case for women of low parity and by and large primigravidity, who carry the large proportion of this burden of pregnancy associated malaria. And when an immunologist sees a graph like this, he or she will, I think in many cases, immediately start thinking acquired immunity.

I did and other people have done that before me, and if that is really the case, the question becomes, why are these women not immune to these kinds of parasites even before they got pregnant? And the answer to that question was really first suggested by a paper published by Steven Rogerson, showing that the parasites cannot only bind to various protein molecules, but can also bind, in some cases, to unusual proteoglycan molecules, such as chondroitin sulfate A. But it really took off when Mikhail [misspelled?] Freed and Patrick Duffy the subsequent years showed that parasites obtained from the placenta exclusively bind to this chondroitin sulfate A molecule, and very rarely bind to other molecules that are

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

often exploited by the variant surface antigens expressed by parasites causing infection in non-immune individuals; clearly suggesting that the parasites causing problems in the placenta are functionally completely different from parasites causing problems in non-pregnant individuals.

And this brings me back to the hole in the antibody repertoire that I left a few minutes ago, because we think this remaining hole here is really associated with pregnancy-associated malaria. So if you would go to the next slide.

We now believe that as a woman becomes pregnant, she acquires a placenta, of course, and this placenta then opens the opportunity for parasites that can bind to the proteoglycan molecule chondroitin sulfate A to establish an infection, something they couldn't do before she got pregnant. And since she has no pre-existing immunity to this parasite, although she is pretty much protected from all other kinds of parasites, she will, if she is exposed to parasites, develop pregnancy associated malaria.

For this model to work, that really requires that the antigens associated with pregnancy associated malaria, those we call VSA [inaudible] are not only functionally distinct, as I showed you previously in the ability to bind to CSA, but that they are also immunologically completely distinct from all other variant surface antigens, because we require for this

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

model to work that she does not have any antibodies to these kinds of antigens prior to her first pregnancy. And in the next slide, I will try to convince you that that is indeed the case.

We have here parasite expressing any variant surface antigen not associated with malaria, shown in the blue part of the graph. And if you take such a variant surface antigen and start to look at antibodies with specificity for such an antigen in malaria exposed populations, you will find the men and women have roughly the same levels of antibodies to such variant surface antigens. You will also find if you go and look at pregnant women or women who have been pregnant one or more times, that it really does not matter how many times she has been pregnant in terms of the levels of her antibodies with specificity for this variant surface antigen that is not related to pregnancy-associated malaria.

Of course, the interesting part of the graph is not the blue part, but the red part here. Because if you take a variant surface antigen associated with pregnancy-associated malaria, and that could actually be taken from the same clone of parasites as we used in the blue part of the graph, than the picture changes in a striking way.

Antibodies can never more be found in men. Even though they have high levels of antibodies recognizing the variant

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

surface antigens not associated with pregnancy, men do not have antibodies to parasites expressing parasites that bind to chondroitin sulfate A or parasites that can be obtained from the placenta. Some women do, not all of them. We think that those who do are probably those who are or have been recently pregnant.

Also interestingly, if you go and obtain plasma samples from pregnant women, you will see that there is a striking relationship between the levels of antibodies, this specificity for the pregnancy type variant surface antigens that you never seen over here. So the variant surface antigens associated with pregnancy are clearly both functionally different binding to CSA than other variant surface antigens, and also immunologically different documented by the inability of men to recognize such antigens.

This is in itself, I think, immunologically interesting, but it would be even more interesting if we could link this kind of observation to the actual protection to the clinical consequences of pregnancy-associated malaria that I talked about in one of the earlier slides. And if we can go back one slide, possibly. That is not possible? That is not possible, it appears. Anyway, I will try to convince you, even without the help of the—I will try to convince you that this is actually the case without the help of the slide.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

We are shown in a study published in the *Lancet*, that if you compare the level of material anemia in women with high levels of antibodies to the pregnancy-associated antigens and women with low levels of antibodies to these pregnancy associated antigens—here it comes—shown here. I hope you caught the gist of it. It's a small one up here that I'm trying to discuss. Women with high level of antibodies, with specificity for the pregnancy type antigens, shown in green, compared to women with low levels of such antibodies, shown in red, women with high levels are substantially less anemic than the women without such antibodies, and effectually protects them from acquiring or having what we call severe anemia in pregnancy where the borderline is usually set around 8g/dcl.

In exactly the same way, if you compare women with high levels of the pregnancy type antibodies to those without such antibodies, women with high levels give birth to children that are substantially bigger than children delivered by women without such antibodies, and effectively lifts all of these women out of the risk of delivering a low birth weight child where the border is usually at 2.5 kg.

Perhaps we could go back to the slide that was so eager to be shown. It becomes then interesting, of course, what this variant surface antigen associated with pregnancy-associated malaria is in molecular terms. And there is an increasing body

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

of evidence that suggests that if not identical with VSA [inaudible], then at least one particular PfEMP1 molecule, an unusually restructured molecule residing here in the figure that was shown to you even yesterday by Daniel Carute [misspelled?]. This molecule is at least very important molecule of the VSA [inaudible] type. Next slide, please.

So I hope I have convinced you why pregnant women are so susceptible to become infected by malaria parasites when they are pregnant. But then another problem crops up. Because if there are so many parasites in the placenta of these pregnant women, why is it so that congenital malaria or early infancy malaria, an endemic area, is so rare as it actually is? And you don't have to take my word that it is rare, because I can show you in the next slide, in a study done by one British military doctor back in the '50s had the good sense to sit down and put together a summary table of a lot of previous studies probably also done by British military doctors working in the tropics.

And as you can see here in the right part of the slide, they found that a lot of women were infected with malaria when they were pregnant, and a lot of their placentas were chock full of parasites. And yet, if you look at these children, the infants born by these women, you hardly ever saw any parasites. And I would think this is a bit strange. Whether the parasites

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

are able to cross the placenta during the pregnancy, which is a bit contentious, but for sure if you have a placenta full of parasites, it should be very likely that some of these parasites gain access to the infant circulation as all the membranes rupture during delivery.

If we look at variant surface antigens perspective to these things, then, however, it becomes quite simple in a way. The woman is, of course, susceptible to her placental infection because she has no pre-existing immunity to particularly those parasites that bind to chondroitin sulfate A, and can bind to molecules in the placenta, as shown here. These parasites, however, even if they are put into the infant by accident either during gestation or during an accident of birth, cannot exist in this baby because babies don't have placentas.

Should this parasite realize this to [inaudible] and manage to switch to another non-pregnancy type variant surface antigen before it's too late, it would not help it really, because the mother has taken good care of her child even before it is born by providing it with substantial passive immunity to all the variant surface antigens that are not associated with pregnancy-associated malaria. So we can reconcile this conundrum of susceptibility in the mother and resistance in the baby.

I will now turn to the last of the five questions and

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

you will be relieved to realize that I will deal with that with some expediency. But it has been actually a puzzling and very frustrating problem for malaria immunologists that it has been so exceedingly difficult to come up with any immunological assay that can tell us with any certainty whether a given individual is susceptible to malaria or protected from malaria.

We have lots of assays that will be able to give us some indication of the level of protection at the population level, but we cannot really at the individual level see whether an individual is likely to be protected or likely to be susceptible. Why is that? I can think of at least two fundamentally different answers to this question.

First of all, it could be because the immune response studied is not causally related to protection. And with the utmost respect, I suggest that that might even be the explanation in many cases. However, it could also be that there is some intrinsic feature of an immune response that is causally related to protection, but which makes it very difficult to demonstrate such a relationship. And I think that that is part of the explanation when it comes to variant surface antigens, as I have tried to illustrate in the following slide.

I have tried to draw three different people. They're not very nicely drawn, I'm sure, very schematic people here.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

But the idea is to illustrate a person with very little immunity, a medium, semi-immune individual, and a highly immune individual. Each of the little boxes here represent a variant surface antigen and the color of each little box represents the level of antibodies to this particular variant surface antigen the individual has. So this person is really graced with all the high level of antibodies to a single of these antigens.

So if we look at some antigens, you will find if you choose one of them in random, sometimes you will find absolutely no relationship between antibody levels and protection. For example, in this case here, all of them don't have antibodies to this particular variant. And down here, you will be even more frustrated, because there is some variation, but it is not related to protection.

You could be even more frustrated if you were unfortunate to use another variant surface antigen, such as this one, where you will be left to the horrible conclusion that having antibodies to this particular variant surface antigen might be bad for you, which I think would be a wrong conclusion, but a tempting one if you looked only at this single variant surface antigen.

And finally, you might just get lucky in your days and you find one where there is a relationship between protection and antibody levels. The question then becomes, which of these

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

should we look at? And that, I think, is going to be a major challenge for us in the years to come.

So actually, I would just like to draw your attention to this paper here that we published some years ago, because in that paper we look, actually, at antibodies to different variant surface antigens, and tried to relate those responses to clinical protection, and found that some of them were indeed related to protection. Whereas, there was no shred of evidence that others were relate to protection.

So you can now have some relief. I will be over in a few seconds.

I'll just summarize the questions that I have raised and my attempt at answering them. Why do only some parasites cause severe disease? We believe that only those parasites to which you do not have pre-existing immunity will be able to cause disease in you.

Secondly, why is it easier to become immune to severe malaria? Why do you become immune to severe malaria before you become immune to uncomplicated disease? We think that that is because in a non-immune individual, parasites that express variant surface antigens that tend to lead to severe malaria will dominate.

And thirdly, why is it a problem in terms of malaria when you become pregnant for the first time? It's a similar

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

answer really. It is a problem because you will make yourself susceptible to parasites to which you have no pre-existing immunity, parasites that can bind to chondroitin sulfate A in the placenta.

Fourthly, why is congenital malaria so rare, while pregnancy-associated malaria is so common? That is because of passive transferred VSA specific immunity kindly provided by the mother to her offspring, and the inability of that parasite expressing the pregnancy type variant surface antigens to thrive in the infant who obviously does not have a placenta.

And finally, why is it so difficult to predict protection at the individual level? We think that this may well have something to do with what you could perhaps call the Monte Carlo nature by which variant specific immunity operates.

And with these words, I would like to thank you for your attention by just acknowledging in the next slide the people who have been so kind as to foot the bill for the research that we have been doing in Copenhagen over the years; and in the last slide, by acknowledging all my colleagues in Copenhagen who have done most of this work, and some of whom are shown in this slide, and many of who are actually present at this meeting; but also, of course, my colleagues all over Africa and even elsewhere in the world. And this these words, thank you for your attention

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

[Applause]

**ROSE LEKE:** Lars, thank you very, very much for this very well, very comprehensive presentation, and showing all of us the importance of VSA, as you take five questions that are so important to immunologists, and you tried to give us a clear picture so we can think about it more and discuss it better. And so, knowing that we don't have too much time, can we have some questions. I know there are some people with some real burning issues. So, please, can we take the questions.

**MAX:** There is a contradiction in your presentation. When it comes to the surface antigens, in the case of severe malaria in the woman, in the placenta, you say that there is a specific variant; there is an archetype of the parasite; there is a certain [inaudible] in the kid, in the child; it's random. I wouldn't agree to that. I would say that in the child there is also the case of being something specific, maybe not one, but maybe archetypes of sequences that causes severe disease. What do you say about that?

**LARS HVIID, Ph.D., Sc.D.:** That causes a very pertinent question, and I suspect Matt already knows that I am in absolute and total agreement with him. And I didn't really go much into the issue of which variant surface antigens will cause severe disease in infants and which will not, is an intriguing question that we are dealing with with some

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

concentration. And I think that really is a major challenge to try to [inaudible] the variant surface antigen into those that are liable for severe disease in children and those that are not.

**MATT:** But you didn't say so. You said that one was the [inaudible]. You said, I mean, more or less like Karen said yesterday, it's a random phenomena. And then in the pregnant, there is a specific event. But you don't think that?

**LARS HVIID, Ph.D., Sc.D.:** No. I love and respect Karen, as everybody knows, but again, with the utmost respect, I [inaudible] with her interpretation of things. So if it came across as if we were in agreement on this one, I'm very sorry an very thankful to you for clarifying the message.

**MALE SPEAKER:** I have a question about pregnancy-associated malaria. How could we [inaudible] these observations and to other observations first. [Inaudible] and secondly, how could you explain that [inaudible] after delivery during [inaudible]

**LARS HVIID, Ph.D., Sc.D.:** Two important questions. The first of them, why is it—because I told you that pregnancy-associated malaria is really restricted to primagravidity, and if I have to be really honest, that was a lie. It is true, however, that it is greatly concentrated on primagravidity. It will be very much dependent on the intensity of transmission in

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

the area that you are studying. If you are working in an area with very high intensity of transmission, pregnancy-associated malaria will, by and large, be restricted to women of very low parity. If you move into areas of lower [inaudible], it will be more spread out. That said, I can [inaudible] already coming back to the microphone, but I will continue a little bit before I give you the chance.

Just because you're pregnant, there's no guarantee that you will be come infected during that pregnancy, thank goodness. So you may actually just be a lucky person who managed to go through several pregnancies without becoming infected during those particular nine months. And thus, although you may be pregnant for the fourth time, this fourth pregnancy may be the first one where you'll see malaria parasites, and you will thus be functionally pregravid at the time.

So, turn to your other question. I have to deal with the questions, otherwise my memory is short. So I have to deal with the questions as they come. The other question was why is it, which has been demonstrated in several studies, that women are also at increased risk of infection and disease during the postpartum period? And I have no problem with that. I don't think that is really what I would call pregnancy-associated malaria, as the woman is no longer pregnant. And we know that

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

parasites causing the placental infection in pregnant women, these parasites go away as the placenta goes away. And I think what we see in the postpartum is a consequence of women who are undernourished, and even put a lot of stress by a nursing baby and a horrible husband, for sure also, and therefore, being very susceptible to succumb to all sorts of bad things.

**MALE SPEAKER:** The observation has been made [inaudible]. It's clear that there is no [inaudible] during the pregnancy and after. But with that said, [inaudible]

**LARS HVIID, Ph.D., Sc.D.:** I'm not sure I'm aware of those things. Perhaps we can discuss them later on. But our observation is that as pregnancy progresses, there is a tendency for antibody levels in general to go down. And that goes for non-variant surface antigens and for variant surface antigens alike, with the exception of the pregnancy type variant surface antigens that tend to go up as pregnancy progresses.

**FEMALE SPEAKER:** I think we can reconcile what you consider to be different points of view, in the sense that I think you're concentrating on that which is common, and I'm concentrating on that which is rare. I want to make a specific comment on your presentation. I think you can explain a lot of what you're seeing by imposing hierarchy on the expression of the variant surface antigens. For example, those that you are

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

seeing to be associated with severe malaria might be those expressed early in hierarchies. And if you think about the pregnancy situation, what is actually going on in those women is all of the parasites in those women have [inaudible] to CSA, all the parasites are working through a repertoire of variant surface antigens, and potentially ending up with [inaudible] CSA. So it's the end of the line; and that's why all parasites that you see in the placenta are at that time.

**LARS HVIID, Ph.D., Sc.D.:** I don't particularly disagree very much with what you say. Perhaps I would, however, say that if you see the ability of parasites to bind in the placenta as the pinnacle of the whole thing, perhaps it could be the other way around. Because many parasites that do not have PfEMP1 molecules, can bind to CSA. So maybe that is where it all started.

I have been told by the chairperson that I must leave the podium now. I will be very happy, of course, as you know Karen, to discuss with you at any length you may want. Thank you.

[Applause]

**ROSE LEKE:** Lars, thank you very much for this presentation. Lars is the head of the Scientific Organizing Committee, the Scientific Committee for this meeting. We've also enjoyed his real excellent presentation, and he did so

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

much work. Can we give him a hand for everything he's done, also for the presentation. Thank you, Lars.

[Applause]

**PETER NDUMBE, M.D., Ph.D.:** It gives me great pleasure to introduce our next speaker who will be talking on ethical perspectives in malaria research in Africa. Our next speaker is Professor Wen Kilama, who was born in Tanzania; studied biological sciences in the U.S.A.; and did his Ph.D. thesis on genetics of muscular susceptible to malaria. When we turned to Tanzania in 1970 and founded the Department of Parasitology and Medical Entomology at the Faculty of Medicine, the University of Dar es Salaam. In 1980, he founded the Tanzania National Institute for Medical Research, which he led for 18 years. On retirement, he founded the African Malaria Network Trust, AMANET, of which he is the managing trustee.

His earlier publications on malaria were on the parasite disease, and lately, his interests have shifted to health research ethics in Africa, a subject that he will be addressing today. And perhaps I will just make a very quick comment before I hand over the floor to Wen on journalists. Because it's important that we work with them in order to be able to carry our message across. And I will just refer to Ambrose Bierce, who was an American writer and journalist, and you will see that they do not always say the wrong thing.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

For example, Ambrose defines a brain as an apparatus with which we think. I think that is okay. And he actually defines a sweater as a garment that is worn by a child when its mother is feeling chilly. That also is okay. And he defines a year as a period of 365 disappointments. Wen, come and talk to us about your successes. Let's give Wen a hand, please.

[Applause]

**WEN KILAMA:** Thank you very much, Peter, for the nice introduction. As Peter pointed out, I led my earlier life doing research on malaria, like most of you have been doing. In the 1980's, and 1990's, for 18 years, as he pointed out, I was the director general of the Tanzania National Institute for Medical Research. And in that position, I was in an enviable position of approving research that was going on in Tanzania. And as you may have seen, there have been many, many studies coming from Tanzania, and during those periods, I was the man who was in charge of that.

So it was through these interactions that I found that I had to know ethics, otherwise, one may have studies that may not be ethical and [inaudible] in the country. So like most of you, I'm not an ethicist. I only acquired the label in the last, maybe, 15 years.

Now, my presentation has the contents that I researched. I shall start off with an introduction. Go

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

through asking why are there concerns. I will go on to the regular issues of informed consent, standard of care, benefits and risks. And because a lot of people who are entomologists usually say, oh, I'm only working with mosquitoes, and there are no ethical issues, I shall go over that. I shall also go on to the area of when research is over or when a trial is over; then I look at issues relating to ethical review; and then I shall go on to the way forward.

Now, a lot has been said about malaria. In this slide, I'm going to present several quotations. The one that you're familiar with says, malaria is public health problem number one, public health enemy number one. A recent one given by two people, Jeff Versats [misspelled?], and I think also someone in this audience, says, "Malaria, Africa's silent Tsunami." Another one says—this is also by Jeff Versats—that "Malaria is the greatest chuckle to Africa's socioeconomic development." Without malaria, maybe we'll be much better off. And then yours truly made this comment at the International Congress of Tropical Diseases in Malaria in [inaudible], and this was way back in late 2000, I said, "The malaria epidemic is like [inaudible] Boeing 747s with the children each day, then deliberately crashing them into Mt. Kilimanjaro." And this is really the concern that we have.

Historically, this malaria is a havoc which kills 400

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

times more people than did 9/11 on New York City. Yet the devastation in New York City has changed world history. And if I may quote someone else that says that the population suffering from malaria each year is greater than the population of the United States of America, Canada and Mexico combined. I don't know the population of Europe, but probably we're talking about the same magnitude. So malaria is really a big problem. And yet, malaria remains a statistic. We sit here, we stand here, we say, more than a million have died each year and every year. Five hundred million cases, and we keep it as a statistics. And my feeling is that we need to pay great attention to it. Why isn't that attention being paid, or why is it late? Is it because it kills and maims impoverished, poor communities? Is it because it kills worthless infants, young children and young pregnant women. Thanks, Lars, for the presentation that you made a minute ago. Is it because its effects are worse in rural areas, where access to health care is limited? Or is it because traditions make at risk groups more vulnerable? Or is it because our research participants [inaudible] vulnerable groups? Among those who are most vulnerable, that is children under five, and young, pregnant women.

Then why should we do research? We are doing research, as we have seen throughout this week, because of the failure of

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

the safest and most affordable [inaudible]. We relied on [inaudible] for a long time, and we relied on [inaudible] alone, and we now see the difference. We abandoned the [inaudible] even where it was promising. We abandoned [inaudible] even where it was successful.

If you look in the literature, you will find that there was successes; for example, with each of [inaudible] in areas such as the [inaudible] of malaria transmission, in high altitude areas, in islands of the Indian Ocean and the Atlantic, and also in forest areas. The pretext for abandoning the [inaudible] control was mostly because of perceived insecticide resistance. At that time, there was not much evidence on insecticide resistance. And then some came up and said, this is unsustainable. And you have to remember that this came during the late 1960s, after our independence. And you have also to remember that Asia and Latin America, continue to [inaudible] control, and they had more malaria than we did. But now we see the difference. We have much, much more than they do.

Then why research, I continue? We need research to sharpen existing [inaudible] and malaria tools. We need research to discover, to develop and deploy new [inaudible] tools. And one major area that we have heard throughout this week is that there are many new discoveries that the genomics

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

revolution that is now at hand is revealing leads to new tools. And some would say, we also need research because we are concerned of the current [inaudible].

But as we do all of this, we have to remember the ethics tenet that research has to answer to the health needs of [inaudible] populations, not that it is [inaudible] or being fired. Next.

Why concern? Why am I concerned? And why are other concerned? [inaudible] We are concerned because all clinical and field studies involve humans. We are concerned because historically, it is such as abused research participants. So, therefore, we need to protect these research participants, otherwise they get exploited. We need to be more concerned particularly in the ethical involvement because we are dealing with the very, very vulnerable groups. They are vulnerable because of ignorance; they are vulnerable because there is rampant poverty. You can imagine in a community where somebody is only making a dollar a day, and you come into that community with an offer that you'd be doing research with them, and there's a memorandum of understanding that by participating in this research you will get free treatment. Whatever you do, these people are for themselves for that treatment, for participating in your research.

These are vulnerable groups also because human rights

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

abuses are [inaudible] in Africa. We have some of the outrageous human rights abuses, which we don't even think they're abuses, to the deny a child of education; to deny a woman of the rights of the woman. These are human rights abuses, and to these you can add some of the other atrocities. We are vulnerable also because health systems are weak, and they are poorly managed. And we find not too frequently, research being undertaken in [inaudible] when these people or the workers are diverted from what they'll be doing. And we are vulnerable, not just the system or the people, but also our research systems are vulnerable.

When I was director general of the National Institute for Medical Research in Tanzania, and you remember this was mainly in the 1980s when the country was very poor, and I was trying to set up a health research system in the country. It was unthinkable that someone would come in with a big research project, and I would say, wait, let's make sure everything is in order. So this is the vulnerability I'm talking about, that even in my leadership position, you'd make sure that this project must be undertaken because there might be a ten percent institution overhead when you are getting [inaudible] from your government.

Now, when you go through the literature, and from the consent, there is a [inaudible] aspect of undertaking health

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

research anywhere in the world, and this is all the more important in malaria research because in this case, we are asking ourselves, who are the most affected individuals? Who are the individuals who are going to be participating in research? The most affected groups, we have been hearing throughout the week and in much areas of [inaudible] malaria and hyperendemic is under five and pregnant women.

And as we just heard, these would be primagravidity. Next [inaudible] gives genuine informed consents. This is particularly the case anywhere in the world when one is considering an under five. Even pregnant women in some of our cultures, particularly when they're newly weds, they face the veto power not only of their husband, but also of the mother-in-law, and in some cases, even of the extended family. So in order to get informed consent, these must also be considered.

And when we have young children and even some pregnant women, [inaudible] consent given by the guardian is essential. The situation of the girl child is worst than of the boy child. And I'll [inaudible] by young pregnant women is usually at stake.

And now, let's look at consent in an African setting. The western cultures emphasize the individual in society. And of course, this is creeping also into Africa. African cultures emphasize the social urgency. I belong not only to my wife and

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

my children, but to the family and the extended family and the clan. In Africa, the consultation of family members is therefore of crucial importance, as is consulting communities, and then getting community assent or community commission. And as is becoming clear, I was asked to look at this since the last MIM conference, consent as a process is getting lots of emphasis. And what has also come out in the last few years, it is now being sort of agreed in most of the guidance documents that verbal consent who has signatures are not demanded, is now being accepted as shown in those three guidelines.

An aspect of ethics that has become quite prominent over the last few years is the issue of standard of care. I ask, is it universal? Some people demand that it be universal. Thus, what you give in this sponsoring country, let's say if you are from Harvard or Amsterdam, that it is universal, so you must give the same kind of care. This is a question. That actually came to the front not in malaria, but in the studies that were undertaken on AZT in Uganda.

In malaria, the standard of care is an issue. For example, when we look at the area differences in anti-malaria [inaudible] susceptibility, we see that there are area difference. Now, which of these do you use as a standard? An issue that some of you who are members of Ethics Review Committees are likely to face is that because of the infusion

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

of massive funds [inaudible] quite a number of problems, like verbal [inaudible] for malaria, TB, HIV. Many ministry of health policies are making ITNs standard of care. And I will not be surprised if some Ethics Review Committees would demand that a standard of care is ITN, and this should not be denied to research participants.

But the question that is now getting to be quite a problem is, who should provide this care? Is it the sponsor? Is it the researcher? Is it the minister of health? Is it the local government? These are questions we have to ask ourselves. So then, we ran into dilemmas regarding standard of care. Who should provide non-routine care? This is getting to be a problem, particularly with the advent and spread and intensification of HIV. Who should do this, for example, where an individual is HIV seropositive at baseline? How about the individual, let's say you are doing a malaria vaccine baseline data, [inaudible], and someone [inaudible] during the trial? When are you going to provide antiretrovirals? Is it because someone is seropositive? But in Africa, they say that is not quite what it should be. How long are you going to provide the [inaudible] researcher? How about for other elements? And this gets worse when one considers chronic diseases. Is it the malaria researcher who is going to be taking care of chronic diseases, if, let's say, the individual has diabetes?

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

Let's now look at the personal benefits and risks. And what we usually say is we must in all research, balance benefits and risks. What then we ask ourselves are the risks that are inherent in many of the new research activities we're undertaking? For example, if there is a [inaudible] vaccine formulation, on Friday morning, at the Bio-Ethics Symposium, I think it is Aaron Sal [misspelled?] is going to address that, as also [Inaudible]. Remember, we are going at one time to be dealing with the children. We are going to be dealing with pregnant women. This is why this is important. Even in western countries, experience with novel vaccine formulations, whether it's DNA vaccines or [inaudible] or whatever, there is very little experience with those, no adjuvants, AS02, all of this, there is very little experience. The question of age [inaudible] we are talking about a vaccine for an infant. And yet we say, it starts with the adults.

I have no problem with the adults. We [inaudible] to let's say [inaudible] in a youth, but then when you get to the children, the children cannot give informed consent. You know that gets to the infant child. So these are some of the questions. There are also risks to be considered with the transmission blocking vaccines, which, yes, we hope they'll protect the community, but how about the individual who receives that vaccine, what benefit does he get? Unless, of

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

course, you have very wide coverage.

There is a question of trials in countries of origin. The one in which we call 1A/2A trials. There is no malaria in Europe. There is no malaria in the United States. Should we insist, as is shown in quite a number of documents or guidelines, that these trials must always start in the country of origin. This is a major ethics question, but I think that is going to be covered by someone else or at the Friday symposium.

There is the question of [inaudible] prospecting. We know there is a lot of biodiversity, richness in bio-data in much of Africa. We know. We have people, ethnobotanists, who study [inaudible] malarias. We are told their results cannot be patented because that is already common knowledge, and that is not patentable. Yet someone from the west can take that same information, take that same anti-malaria and turn it into a patentable product. So that is, yes, bio-prospecting, which [inaudible].

How about material transfer agreements? When I was reading the research in Tanzania, at that time there were no material transfer agreements. Someone would come to my office and I'd give them—I would sign documents saying, this is of no economic [inaudible]. It can be exported outside of Tanzania. And in many African countries, so far lack material transfer

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

agreements or protocols that would protect that biodiversity.

As I said earlier, our entomologists, when you ask them about ethics, they'll say, oh, this is [inaudible]. There is no ethics involved. But we have to remember when the research starts. In my early days, we used to catch mosquitoes with what we call "human bait." Is that ethical? Now, we have to also remember, which is really unfortunate, there are a lot of guidelines, very many guidelines, by [inaudible] by the [inaudible] Medical Association, by the National, by Ethics Commission in the U.S., the European Commission, and so on, every so many years we get new guidelines. How about when it comes to ethical review of epidemiological studies? The latest letter I'm familiar with is 1991. I hope there will be a revision of that soon.

I already mentioned mosquito collection human bait. Now, the questions that are raised, and which we have not been paying sufficient attention to. Late, for example, questions of community assent, but also not forgetting that we should actually get individual consent. If we have household entomological studies, these will need not only just going in and spraying and [inaudible], but that there will also be the need for individual and family consent.

There might be community [inaudible] interventions. These will need individual and community consent.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

So one may say, in entomology or epidemiological studies, [inaudible] studies, do I need the standard of care? Yes. In this case, we will need to provide best available intervention. Then [inaudible] would ask, when we started undertaking ITN studies in the 1980's, and then they became bigger in the 1990s, what was the best available intervention during that time period? You would answer and say this was [inaudible]. Did we actually undertake studies where we compared [inaudible] with ITNs? We did not.

Now we are talking of scaling up the use of ITNs. And yet we are relying on only one [inaudible]. Is it ethical to just—we [inaudible] for treatment, we know the results. Now, we are seeing [inaudible]. We know their mode of action does not differ much. Are we hearing not putting all of our eggs in one basket? Don't we mean to actually alternate different types of insecticides and the different modes of application, and different modes of control?

Risks and benefits. I don't need to mention environmental pollution that would result in environmental pollution, that would result in [inaudible]. But we must balance the risks with the benefits.

How about genetical [inaudible] mosquitoes? The transfer of transgene to [inaudible] organisms, we have to watch out for this. The question that I [inaudible], at least

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

in my country, where we have been in the forefront in the ITN's, our [inaudible]. But when it comes to getting the benefit, is it the rural areas who get the benefits first? Do the mechanisms or the methodologies that we use in promoting the use of ITNs targeted at rural people when we advertise them on television, and there is no electricity in the village?

So these are questions that we need to pay attention to. And if we are talking of, let's say, genetic modifications, if we are talking of releases, rumors is usually a big problem. At least in the 1960s, when I was a university student, for example, in the countries like India, the release of genetic [inaudible] mosquitoes [inaudible] the consent. And this was fueled by the media. And this we should know, if [inaudible] consent, then you are cutting down the cohort. So the cohort you intended in the beginning, you cannot actually achieve it at the end.

The question of management of adverse events, those of you who are working with DCP, also comes in. Let's say, for the risks, goes wrong, what do we have in place to actually take care of adverse events? The big problem of ethics [inaudible] provide successful products. This is a major area in ethics to me. You have [inaudible] to an area. You have been able to use insecticide [inaudible] nets, and have achieved a very good level of control. Your research is over.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

You pack your bags and go. The rebound effect is a major area to consider.

Then let's say continue with [inaudible] research or the trial is over. Let us remember that, unfortunately, the malaria problem still remains. You are finished your research. The malaria problem is still over. The minister of health, the local government, we are probably not prepared to take care of— I mean, they are not aware of the situation, but now you are putting them in a situation that they are compelled to act. And you may find that access to the product is going to be limited, and the question comes in who will make that product available. Is it the Minister of Health? Is it the sponsor? Is it the researcher? Or should we be thinking before we undertake the research of this question, who will make the product available and put this in a memorandum of understanding right at the beginning of the study?

Now, the question is, if you so make it available, you are still in a dilemma for how long and how far. This is a major question: how far? You came; you used your epidemiological methodologies, randomly you choose that village, you choose that community, you leave the other community; they're not prepared to participate. And [inaudible] I will make the product available only for you and not for the other group.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

When the research is over, the literature coming out is that successful product to be available, we need to involve public/private partnerships. And I will further say that we need to link bilateral research sponsors with bilateral donors, and have listed some examples. What I'm trying to say is that if, let's say, NIH, has funded a project, we know they are not allowing it to get into health care. But if their successful results could be passed along to [inaudible] implement, then down the line, if it is MRC [inaudible] Canada, [inaudible]. And we need to mobilize philanthropy and private funding.

When the research is over, we have to ask, or it has always been asked, what is owed to the sponsor. This is very clear when you read [inaudible] documents. This is clear because this [inaudible] documents were actually, many are prepared by industry. But what is owed to the PI? That is not very clear. And then what is even more confusing and usually completed absent is what is owed to core investigators, particularly the other researchers, the junior researchers, the assistants, the host study [inaudible] and the study communities. What is owed to them is usually not clear. And indeed, it reminds me during our days, we used to talk of colonial trade model, where we received trinkets for ivory. They took the ivory and they gave us maybe something to wear around our necks.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

When the research is over, is completing research a means to an end? To get our publications, our promotions, our accolades, and to move to greener pastures. Where I didn't do that, I was able to stay in my country [inaudible]. But we have to ask ourselves, what happens to [inaudible] workers. There are questions relating to authorship, international interviews, their information dissemination [inaudible]. We rush to go to BBC; we rush to go to CNN. We forget that the research participants are actually the primary, should be the primary target of research results, and by target, it must be in a language that they can understand.

The policymakers, the decision makers, are the health workers. We are unethical. We are not including them in information dissemination. The question of that ownership is something that we don't pay much attention to. We gather the data. Nowadays, you can even gather data which you [inaudible]. It is sent immediately to the sponsor country. And the sponsor institution, which is going to compile that information, and then they said this is what you are going to publish.

[Inaudible] is my last area to cover. This is new to many African institutions. Quite a number of questions still remain unanswered. We ask which institution or which Ethics Review Committee has [inaudible]. Is it the host country

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

Ethics Committee, or is it the sponsor country Ethics Committee?

Another problem in our experience that is ongoing in Africa is the circulation of scientific from ethics review. Should this be two committees, or should it be just one committee. And you have to remember [inaudible] of personnel to undertake to be on these committees, and also the problem that in our countries we know almost one another.

And the question raised also there, there is a tendency to say, oh, in my country, these people are poor, and so on. You gloss over the ethics review. My feeling is that maybe we should—wait, not maybe. We should be more stringent because these populations are very, very vulnerable.

Another question that is coming up is the question of who should fund institutional ethical review? And also very, very big problem is the question of weak oversight. In one example, one Texan professor got ethics review and a clean slate to do research in Tanzania. He did the research, misbehaved, but because of weak oversight, this was not realized until this Texan professor started being reported in the major newspapers and on the Internet—newspapers in the United States. And finally, this professor was jailed in the U.S., unfortunately, not because of the commitments he did in Tanzania, but the commitments he did in the U.S.

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

And another big problems I [inaudible] documents are very inconsistent. So those of you who are on Ethics Review Committees have to watch out.

Now, what is the way forward? The way forward, I'm saying, is that we should increase protection of study participants by improving ethics review. We should include African voice in the development of [inaudible]. That experience with new formulations is limited. Therefore, we must be very careful in weighing risks versus benefits. We should also ensure appropriate trial design, informed consent standard of care. We should promote public/private partnership, and we should ensure post-trial obligations.

I'm thankful to the supporters of AMANET. Our major financial supports are the European Commission, [inaudible], the Netherlands Minister of Foreign Affairs, the Danish [inaudible], and for that, I thank you very much.

**PETER NDUMBE, M.D., Ph.D.:** We thank Wen Kilama for this very comprehensive overview from an ethical perspective on research, particularly malaria research. I think that we'll take a couple of your questions. Wen Kilama will be standing by to take a couple of questions.

**MALE SPEAKER:** [Inaudible].

**MALE SPEAKER:** [Inaudible]. So for us researchers, we should be prepared that when you want to export this materials,

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

in this case you are talking of, let's say, parasites in blood, where there is going to be material transfer agreements in place. This there is no question about it. It is coming.

And on the ethical front, the [inaudible]. On the ethical front, there is already quite a movement trying to restrict what goes into the consent form. The open-ended consent form is being resented. So what the Ethics Committee has to watch out for is this open-endedness. And when it is not open-ended, you will find that there will be restrictions on which one can do with that particular [inaudible]. There are going to be some people who are going to use these isolates maybe for purposes, which were not originally intended. This is a problem, but the Ethics Committees which we train are getting aware of this.

In terms of validated clinical trials in Africa, some of us have been trying to make sure that the trials that are undertaken in Africa meet not only scientific standards, but that they meet both ethical and GCP standards. Thank you.

**PETER NDUMBE, M.D., Ph.D.:** Maybe if we can take a series of three questions, and then you would respond at once, if there are any. And just be brief and direct. Okay, there are no forthcoming questions.

So let me say that the ethics discussion will continue on Friday at the [inaudible] Ethics Symposium. So please, make

<sup>1</sup> kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

Plenary Session III: Immunology and Pathogenesis  
and Plenary Session IV: Bio-Ethics  
Fourth MIM Pan-African Malaria Conference:  
Yaounde, Cameroon  
11/16/05

54

sure you are there. And if there are any questions in your mind, you may have the opportunity of expressing them there. So on behalf of you all, I thank Wen Kilama for his very clear talk.

[Applause]

[END RECORDING]