

**Plenary VII: Vaccines and
Plenary VIII: Clinical Applications and Drugs
Fourth MIM Pan-African Malaria Conference
Yaounde, Cameroon
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VINCENT TITANJI, Ph.D.: Gentlemen, my name is Vincent Titanji. I come from Cameroon. We are approaching this session with Dr. Allen Saul from the NIH Bethesda. Interest in research for malaria vaccine has been sustained not only because of the university admonish efficacy of vaccines in controlling infectious diseases but more so because of the ever increasing body of evidence that supports the invisibility of the malaria vaccine.

In the previous sessions, we have heard, reviewed some of the evidence. This morning's session is devoted to a review of the progress made in destine vaccines and by an acclaimed leader in the field Professor Brian Greenwood who will be introduced to you by the co-chair, Dr. Allan Saul, who is another authority in the field. Permit me to say before handing it over to him, how pleasant it has been to work with him in preparing the vaccine development symposium for the MIM conference. During the week, we were reminded that the plastomodian [misspelled?] genome could destroy 5,600-6,000 [inaudible] of which they have some safety, have so far been able to catch it in preventive minute. Seen greater than 40-60 percent of the proteins predicated by the general of unknown function, we noticed whether there is still some critical but similar proteins as yet to be discovered that would make a

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difference to the vaccine development initiative. In the book entitled *Malaria Research in Cameroon*, which copies were distributed to you earlier, we have to try to raise this issue. A few copies of the book are still available for those who received them.

It is now my pleasure to call on Dr. Allan Saul to introduce our speaker. Thank you.

[Applause]

ALLAN SAUL, Ph.D.: Thank you Vincent. Before I introduce Brian, Rose Leake [misspelled?] has an announcement and there will a short film that will be shown before the actual talk starts.

ROSE LEAKE: Good morning, everyone. This morning's plenary has been devoted in the memory of Ebi Kimjanani. Ebi was one of the best scientists we had on this continent. And she was a woman. She draws everything for us. Ebi was science. Ebi was love. Ebi was friendly. Ebi was everything. Ebi was so brilliant, so hard working. And she worked tirelessly. She was working for malaria. She had set up a little broke [misspelled?] to do clinical trials to follow and monitor clinical trials in malaria and went from one part of the continent to the other. And in doing all of that, what happened. She got malaria and she died at the Montreal General Hospital on the 23rd of January this year.

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So, we have a few pictures in memory of Ebi that we all should remember her. I think we all who knew her keep pushing on, moving on because we know there is a voice that is telling us, driving us to move because Ebi would never let you rest. She just had these rules that we had to do. She was a wonderful companion as a woman. We have to do the science for Africa. We have to do everything we are able and she just kept us going so I won't be long. I just want the pictures to go through so please have them on. That is Ebi with her family in Montreal. Drew gave us these pictures. I was looking for him, I don't know if he is in the hall. He knew these pictures better. Yeah, that is Ebi and her son. She had two children and they are in Montreal with their dad. She was from Kenya so that is her and her dad. [Long pause as video runs.] That was her last visit here. [Long pause] So, that is Ebi and she died of malaria like I said at the Montreal General Hospital January 23rd this year. Could we all stand up for a minute of silence, please? Thank you all very much.

ALLAN SAUL, Ph.D.: Well, it is now my very great pleasure to introduce Professor Brain Greenwood from the London School of Hygiene and Tropical Medicine. This must be surely one of the easiest introductions to do it for the whole meeting. Many of you will know Brain. He has been a very prominent research in the field of tropical medicine in general

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as well as malaria in particular. Brian has had a one of these unusual beings with this very broad interest and what is perhaps even more unusual, not only has he a very broad interest, he has a very great expertise covering the wide variety of fields. Of particular relevance this morning, Brian has worked in the field of vaccines, vaccine deliveries, vaccine testing in Nigeria, Gambia, and I think he is uniquely positioned to give us an important view of how vaccines made impact on the future of malaria control in Africa and in the world. Thank you Brian.

[APPLAUSE]

BRIAN GREENWOOD: Thank you very much Allan and Professor Titanji and thank you all very much for coming on Friday at the end of a long conference. I think we are all tired and I am so grateful that so many people have come. I think this has been a very special week for malaria vaccine development because I think for the first time we can talk about a malaria vaccine. By that, I mean a product that has a real chance of getting registered and being introduced into malaria control as a practical tool. And most of my talk will be about that and how we might tackle some of those issues that rises.

But I am going to start with just a little bit of looking backwards to the history because I think it is

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interesting to know how long it has taken us to get this point in which we have for the first time a real potential malaria vaccine rather than just a candidate antigen that is very promising. But we couldn't be sure it would get registered.

This is 1905, a hundred-year generation, of Robert Koch getting the Nobel Prize. He is best known of course for discovering the tuber bacillus and anthrax bacillus and for evolving Ebutocillus what is not so well known is that he was also a malariologists and he made important discoveries in malaria in the latter part of his life. He probably was the first person really to establish the fact that there is immunity to malaria. He had noticed he had worked both in Africa and in the Far East that adults didn't get so sick though they were infected. He postulated the idea that it was naturally acquired immunity and potentially that we have a vaccine.

But it took another 60 years until that was really established by my predecessors, the director of the University of Uganda [misspelled?] Ian McGregor here who showed that it was possible to transfer immunity from one person to another with gamma globulin, taking serum or gamma globulin, a fraction serum of adults given to children and reducing their parasitemia. So, this was really the first proof that there was such a thing as immunity to malaria.

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The next step came about ten years later when Clyde who you can see here, the zygote is no longer with us, took the first—Chuck made the first experimental slide with malaria vaccine showing that it was possible to protect people by irradiated sporozoites. Also on this slide is one of the early group of people interested in vaccines is P.C. Fullman who we heard about at the beginning of this conference who made just a major contribution to immunology of malaria and pushing along the way to vaccine development.

Was that just a fluke, that experiment using irradiated sporozoites? No, it was not. Dr. Hoffman and his colleagues have recently looked at all the data that they could get about challenge with irradiated sporozoites and the evidence is really convincing in 33 out of 35 people challenged a large number of infected mosquitos. One got protection and in many of those people, the protection lasted for several months. It didn't work quite so well with lower doses but this was a robust series of experiments to show that one could vaccinate against malaria. Dr. Hoffman is perusing that approach still by looking for the possibility of using the pre-erythrocytic vaccine and others are using a attenuated blood stage vaccine. But really, what has been the problem has been trying to find a more practical way of developing a malaria vaccine.

It is not difficult to see why that is the problem. I

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mean the malaria parasite is extremely complex. You have the different life cycles so we have could vaccines against pre-erythrocytic state, either in the sporozoites itself or the liver stage and transmission blocking vaccines. At each of these stages of the parasite development as we heard from Dr. Fereachie [misspelled?] in his very brilliant talk the other day there are innumerable of proteins, several thousand now probably that are expressed. So how do we go from the whole eradicated sporozoite to a more defined candidate that could be used as a vaccine.

I think this just lists some of the different antigens that are being investigated that are chosen and in some cases, it really was by fruit and somebody had an interest in a particular antigen rather than based on a sound biological knowledge of what that protein did.

Now I am not going to talk about vaccine candidate antigens, the different ones, if people are interested I would refer you to this to the locally called the Rainbow Chart produced by Dr. Reed at WHO. This gives an update of where we are with the different antigens, where they are at the different stages of trust. You can't read that part there of what is going. If you are interested in knowing any point of time what is actually happening with the different candidate antigens this is a good place to look. There are probably about

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25, depends on how you actually define a specific candidate, 25 actual candidates now in clinical trials. So things are moving along pretty fast along the pipeline but I think as we have heard this week, there is one candidate that is ahead of the others. This is the vaccine we have been hearing about this week RTS,S / AS02.

This as many of you have heard is a vaccine that is made from the surface co-proteins of the circumsporozoite protein of the sporozoite expressed in yeast with hepatitis B. As I will go through the next slides very quickly because most of you have probably heard these. After a series of challenge studies in the United States in volunteers, the vaccine moved to the field in Gambia a few years ago and gave a very good level of efficacy in adults against infection. But this was fairly short lasting but what was encouraging is when these people were given a single dose the next year, they got some of their protection back again suggesting that the vaccine had induce immunological memory.

The next step as to test this vaccine in children. A year or so ago we got this paper in the *Lancet* here by Alonso and his colleagues from Mozambique which showed that this vaccine really gave quite substantial protection against severe disease, 58 percent, and some protection against infection, perhaps about 30 percent. It is not often that any medical

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interventions reach the front page of the *Times*. And this rightly so was given a lot of publicity.

When these data were, people looked at what was happening here at the end of the Kaplan-Meier curves, there was suggestion that perhaps this vaccine was also waning in its efficacy as had been seen in the Gambian adults. Therefore it was really a big advancement when we heard this week that in fact this protection has been sustained in these children. This is very interesting why it should appear to have been sustained in children but not in adults. I am sure that is going to require further research.

So that is all I am going to talk this specific candidate, how far we have got to one leap candidate, many other different ones are following up behind. In the rest of my talk, I want to address some of the more general issues obvious for all the people working in the field for the epidemiologists. Now we really have to think seriously about the fact that they may in two or three years time is a malaria vaccine to introduce into malaria control. These are some of the things that I am going to address.

So let's talk a little bit first about evaluation and some of this I will try to go over quite quickly because people have been working on this for some time. Just highlighting some of the new things that we have learned

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during the past few years. So I am going to talk about endpoints, how we might speed up the progress of vaccine evaluation and then touching on combinations.

These are some of the endpoints that have been used in vaccine trials. Or at least sorry in malaria control interventions that might have been potentially used in vaccine trials. Starting from the mildest infection progressing down to death and each has its advantages and disadvantages. We have learned some things through first with other interventions like [inaudible] and then the vaccine. Just a few things, I will just a few points about each of these potential endpoints. So first infection, how do we measure that, PCR or microscopic?

We heard in the session yesterday that PCR is now being used widely in China studies done under experimental conditions when people are experimentally infected using mosquitos. But it hasn't yet done been widely applied in the field. Recently we were with Dr. Hill's group in Oxford where they took a study in Gambia which was presented here as a poster, which I have integrated, which looks at the possibility of using baby blood films. And using PCR rather than microscopic as being more sensitive as perhaps a quick way of screening whether a vaccine could prevent against infection. The results are shown here. This is your Kaplan-

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Meier of people free of infection as time passes they gradually are about 10 percent of people are protected. This vaccine didn't actually give any level of protection. What we were using as feed here as a control. And you can see that it was possible within a month to obtain. These differences are significant so we might have been to detect a vaccine effect in that very short period. It is not very pleasant having your finger pricked every day for a month but it is indeed has a strong positive stridulation and was able to get this done. PCR also has another very important role and this is allowing us to see whether a vaccine might have a specific strand specific effect. It varies with the pneumococcus; another vaccine in which people vaccinate against a very variant organism has shown how important that is. That the seven-layer pneumococcal vaccine be used in the United States is selecting out against strands that are not in that factotum and there is a real concern that formed a polymorphic antigen that may happen in malaria. This slide from this London study was done in New Guinea and it showed that was the case. That you received protection here, the Kaplan-Meier has separated against the strand that was used in vaccine but not in another strand. So here, it was clear evidence of a vaccine that is having a selective effect. I think in all future vaccine trials when one has a polymorphic

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antigen, at least in the beginning of initial trials one would have to do this. This has been done without any success in the trial in Gambia; PCR was done to see if there was any selection for particular strands that wasn't the case. That has also been in the Mozambique trial but those results are not yet available.

So, the next stage up from trying to detect infection is trying to detect clinical illness. I think most of vaccine trials were done in field countries. We will use this an important endpoint of some stage in their evaluation. We have learned now that you can do this in two ways. One is by going to somebody's house every day, asking if they are ill. If they have any complaints, you do a blood film and that count as an attack of malaria. The other way is to sit in the clinic with professed case infection when you wait for the patient to come to you. And not surprisingly places are detected by passive case detection are not generally more severe and perhaps reflect more of what would be an impact of an vaccine if it were introduced into public health. So, I am certainly in favor of using this in most situations for your way of detecting an endpoint. But this is very helpful if you have a pre-erythrocytic vaccine and you are wanting to see whether that has an effect on the time to first infection. And I think it is difficult to combine these two together in

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the same trial. And an elegant component of the trial of [inaudible] vaccine in Mozambique was separating these two out so that the two trials were done in parallel one of that case detection and then other in passive case detection.

Now there are suggestions that the RTS,S / AS02 vaccine might progress to a trial with severe disease as its endpoint. That is going to be tough. We heard in one of the sessions from I think Charles Newson [misspelled?] that the SMACK study that has been looking at severe disease across Africa 20,000 cases of severe disease. It is amazing how much variation there is in the clinical presentation between different sights comparing Uganda and the Gambia and so on. I think all of us have been surprised at how much variation there is across sights. So if one is going to do a multi-center trial that is a problem. That was one of the problems of definitions and intra-observer observation. And in the investigation of severe malaria sometimes evolves clinical conditions such as prostration, which is very difficult to define. So if this is going to be used as an endpoint for a vaccine trial a lot of work will have to be done in trying to standardize the classification, especially if the trial is going to be done across different sights. I am sure it is possible but it is going to be quite a task to do that.

Of course the ultimate endpoint is death and it is

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interesting in the Gambian you would talk about the same trial which was I concerned. One thing that everybody has picked on is the fact that vaccine prevented children from dying. And many of the other, equally important endpoints haven't received so much attention. This must be the ultimate thing that we are trying to do with the vaccine is to stop children from dying. Whether that has to be done in a formal trial or whether that can be done subsequentially in a phase four study after the vaccine is licensed is an area that has been much discussed.

Now I have very strong views about using every specific mortality or all cause mortality. I don't think there is any place for using the [inaudible] as an endpoint. the diagnosis of death from malaria has to be made by postmortem questionnaire in most situations. And that is a very crude tool. It was never designed for doing studies like this. It was designed by for giving an overall picture of the pattern of the disease in a particular area. What one would introduce a false classification by doing that and we have shown by—statisticians have shown how even a moderate of false classification could abrogate the effects of a vaccine. You could fail to detect an effect that was really there. So, I think if mortality is going to be used then it has to be all cause mortality.

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The next point I was going to discuss is when you are doing your trial how long should your observation period be. This is a 51. One could get a dramatic success was seen in the Gambian adult trial over a few weeks or a couple of months that either disappear or it is possible you could even get a rebound has been seen in the some of the prophylaxis studies and that for a period the vaccinated children will be worse off. I don't think it is easy to know exactly how or what is the right period that you should make your final evaluation. I would think something around two years should be the minimum that one would want to know that your vaccine provided x-level of protection for that period.

I mean what should—this is what may happen. Your vaccine may wane; you can get a rebound effect. What period should you be looking at? Just this period when you may get a very satisfactory results or for a longer period looking for the rebound. The next slide I think shows what might happen. This is the famous slide Dr. François Trape of the two villages in nearby Senegal one with a very high epidemiological inoculation rate here, one with a lower one. In this community the number of malaria attacks over a period of—over the person's life is the same even though the exposure is greatly different and you can imagine some vaccines pushing this to there. If you look just at this

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period, you would get a 50 percent vaccine effect. If you followed children up to 15 years, you would have no vaccine effect. So I think there will have to be decisions what is a reasonable period to look, at perhaps one or—certainly not just six months but perhaps two or three years. We need to know that if these vaccines are going to be a pride in the field, not just in control, not just as an experiment.

I have mentioned that many vaccines are coming through to the stages of clinical trials and we want to move as fast as we can to get those evaluated yes or no, are they going to be useful? I think we do have to start thinking now if people are interested in doing clinical trials if there are ways in which this process can be accelerated. This is the classical pathway for doing an evaluating vaccine starting up here with your non-immunes going down to a license vaccine here and your phase four studies. This process can take a long time beginning in the prophylactic trial this took ten years from being pursued to here. We don't want that to have to happen with every malaria vaccine that is entering the clinical pipeline.

So what could we do? Well, I think the two areas that could help to cut down on this process is still going to be a lengthy process whatever happens. But these are two things that could happen. One is the de-escalation and usually a

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vaccines have gone through this rather complicated process of safety and reasons of immunogenicity from adults to older children, young children and infants outside of the EPI program and then with the EPI vaccines which introduces other problems of whether the vaccine is going to interact with the EPI vaccines. And I wonder whether we can in fact short circuit some of these things a bit and I think suddenly we can miss out the older children who are not particularly the target of most of the vaccines directed at Africa. Whether you can go straight down from a few safety studies in adults to infants outside the EPI schedule is debatable but that might be possible for some vaccines especially if related vaccines have been shown to be safe. And maybe one can short-circuit this process as well. So I think people will be looking at some of these things thinking what is safe. Safety must always be the first premise but can we speed the process up.

The next slide is really discussing whether we could have surrogate immunological endpoints that would help in vaccine evaluation. That has been enormously helpful in other diseases. Again looking back to the coccal infections like pneumococcus and the meningococcus vaccines have been licensed recently on the basis of immunogenicity alone without a clinical trial to show their efficacy. I don't

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think that we will ever have a sort of malariacidal assay that is equivalent to the bactericidal assay for the meningococcus that would cover all malaria vaccine and could be used as a sort of common denominator but for specific causes of vaccines we may well be able to find indirect correlates that would help very much in speeding up the process on issues such as days and formulation of the vaccine that would prevent going through a clinical trial at each step. We already have some examples when to do this—to do this we have to have results from a field trial to be able to validate these assays but it is beginning to appear that may be some measures for some specific vaccines that would help in speeding up the development process.

So I showed this slide in my first talk about—talking about combinations and I think this is really, really major area because this is going to become increasingly important in malaria vaccine development as well as in malaria control overall both the way we are going to handle the problem of multiple combination vaccines and also the use of malaria vaccines in conjunction with other controlled measures.

What can we do when we have one vaccine that appears promising, another candidate perhaps of derived from a different antigen that also may be protective. How should those be evaluated? I think there are two approaches of doing

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this. One is you do a trial with A alone. Then you do a trial with A + B and A + C and then you sort of build up. Other people have jumped and taken a multi-antigen vaccine, tried that first and then presumably would perhaps deconstructing that and seeing whether you could leave bits out. I don't think we know which is the best approach. Again, that are going to be followed. This is perhaps more eloquent scientifically but may take longer. At this point, you may have a vaccine that works, here you might to have wait until you have gone down the thing to find out if you have a vaccine combination that works. But I think this is going to be a problem that people really do need to think about more and more details, more candidates come along how are they going to be tested in combination.

There will problems to this. There will be particularly ethical problems once any one vaccine has been registered. Up to that point it may be possible to still be able to use a placebo group but after that has happened it maybe necessary to include the license vaccine as well as the one that you are investigating. Then one may end up with very complicated non-inferiority or superiority trials and sort of things. I think that again is going to be something in two or three year's time that have to be thought about. So, what about combinations with other malaria control measures?

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Encouraging wondering around [inaudible] upstairs—the menu is building up with interventions that have been shown to be effective. You could actually add another one from the total care using supplements of zinc and vitamin A.

So where is the vaccine going to fit into all of this? It is not easy to see. I think two major rivals and rivals is not the right word but two main co-control measures that need considering are long lasting. We now have increasing evidence that these next will provide protection for three years at moment that is only epidemiological evidence predominately but I would be very surprised if it was not [inaudible] protection for that line and vaccines are going to be judged against how well would they compare with insecticide treated nets. The other intervention coming along which would take place perhaps in the same age group has children who are getting the vaccines is IPTi and as some of you who came to the symposium yesterday, this is going on quite well with a lot of research activities happening here. That the beginnings of public health have been in discussions as to how this approach to malaria control might be implemented and there is a possibility that if the trials that are currently underway continue to be promising then this could become recommended policy in 2006 or 2007. And that again is going to complicate the rate malaria vaccines

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are evaluated.

I showed this slide again on the first—of my first talk of the year because I think this is really the one slide that I would like people to think about most after this session because I think this is going to the critical issue in evaluation of malaria control measures. This is whether we have one intervention that we know gives you a certain amount of protection when it is tested against the placebo. Another one is you, perhaps a similar amount, in case against placebo what is going to happen when we act them together. Will we get synergy like you get with drugs that their outcome is better than the two individually. Will they just adapt or will possibility will they interact with each other and you may end up you are no better off than just with one or the other. Unfortunately, I suspect that this is going to vary quite a lot from epidemiological situations to epidemiological situation. And really, we are probably going to have to do trials specifically to address some of these questions.

Now these trials are going to be complicated. They will have multiple study groups, not just randomized trials with the placebo that may have to be quite large because we might have to be showing non-inferiority or superiority, the combination of at least one alone. The United States will be

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difficult as I mentioned, there might be ethical problems if they have one vaccine already being licensed. Of course, this will push up the cost of the evaluation. So I think there are going to be really quite difficult problems to address in how to evaluate malaria vaccines and other control measures together.

So how might a cost effective vaccine be used. We may have a license vaccine in perhaps three or four year's time. Well I think it is important that people don't jump to the conclusion immediately that such a vaccine would definitely be used. My reason by that is the next two slides with again with the competitors there are other vaccines coming along and if our ministry of health is particularly keen on vaccination they are going to have to make some tough choices. Do they use a pneumococcal vaccination or rotavirus vaccine or meningococcal vaccine or a malaria vaccine? They may not have enough money even with Gabie [misspelled?] money to afford all of those and some decisions perhaps will have to be made in particularly in community, which will be the most useful. Then also the malaria control program may have to try and make choices as to what they want to use as their control measure. And I think they are going to have choices as we said, long lasting nets, perhaps IPTi and so on.

What is happening again, you have seen literature in

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this meeting shows that under certain situations you cant control malaria effectively using a vaccine. This is from South Africa using the combination of spread and ACTs. That is rather a typical situation. I wouldn't—that is where transmission is very different from the heartland of Africa. But there is recent data coming from Eritrea. I think this is not widely published yet. Eritrea has been glamorizing this and Nyarang'o has given me permission to show you this. This is using conventional control measures, the next effective treatment of this environmental control. So, in this situation, would the ministry of health go for a vaccine? They might not decide to do so. So there are going to be issues there but I don't want to end on a gloomy note. I think there are going to be many situations when a malaria vaccine is the approach tool. But it is going to have to justify its place on grounds of efficacy, costs, and the usual things that we have to do with any malaria control intervention. I think in many situations that we will find vaccines being used. And some of the reasons why they are finding this is the case are shown here. The ones that I think you would like are I think the vaccine does tend to get out in many countries through the disadvantage who have difficulty in getting to health centers, for whom treatment is probably not the best way of doing that. Of course one has

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to face up to the politics and things that vaccine has invoked a lot of interest and maybe able to raise money from the international community that wouldn't be available for other malaria control measures. But any vaccines will have to make their way and show that they are effective and cost effective as other interventions that will be available for use. I think who makes these sorts of decisions it is going to be very interesting how the policy is made or when a vaccine should be used and where and maybe the IPTi can sort in this perhaps providing some help in that in making the pathway through the policy makers of how that decision making process should be made. And I think that this process will have to happen when vaccine has been registered and shown to be effective.

In conclusion, I think it is going to be a very interesting time particularly for the people who are in the next few years particularly for people who are interested in the field side of evaluations as well as those working in the laboratory. We want to try to make this process as efficient and as effective as possible. And the best way of doing that is by people working together and- [Applause] I thought he was bringing them to me actually. [Laughter]

One of the ways that is being discussed during the past year or so has been through the technology roadmap which

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has been sponsored by NBI which has been trying to bring together the broad lax in community to see if we can work together to speed up some of these processes. So thank you very much.

[Applause]

ALLAN SAUL, Ph.D.: We have time for a few questions. Please use the microphones. See Brian I think you have presented such a clear presentation that well maybe you have given people some much to time that it might awhile to digest. I have some questions—there is a hand, yes, please.

MALE SPEAKER: Most of my work has been in vaccines and a vaccine proponent I agree with Brian that when that summarization reaches high levels of coverage there is reasonable equity that most of the data suggests that at moderate to low levels of coverage when we examine the vaccine coverage data by socioeconomic groups unfortunately it is the pull that is still getting. So, what I think what one has to take into account the distribution of vaccine coverage in countries before you can assume that it has a real equitable effect.

BRIAN GREENWOOD: Yeah. That is a fair point, I mean I think once you are actually at 70 or 80 percent coverage then you are getting a bit of a disadvantage or have a better chance.

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MALE SPEAKER: A comment on your message about duration of followup. From as our experience in the vaccine industry is showing us we are increasingly being asked for quite long followup for across the vaccine programs. For example, in hepatitis B we are still which has been introduced now fifteen years, we are still being asked for followup information on durability issues and stability and I don't think that this will be any different in malaria. It is something that everybody involved in malaria vaccine development has to delve into their program.

MALE SPEAKER 2: Thank you so much. An observation of aspect of vaccine production. We know that in 1984 epidemiology of malaria scientific [inaudible] reported that the problems of [inaudible] is maybe a couple and from us to try come with a combination that go together. In 1992, my [inaudible] it was still that important. That is to say that [inaudible] nothing. They were efficient in blocking immunity and [inaudible] but I have not heard you talk about antigen. This world of antigen has it actually solved or began [inaudible] maybe you [inaudible] to us. This is not antigen because they were talking a couple were circumsporozoite, the [inaudible] and the sporozoites. But there has been a problem for that good. If there are cracks, let us know. Thank you.

BRIAN GREENWOOD: Now your question was about antigens

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and I—that is a very fair comment. I mean that is an equally important part of getting your vaccine to work but I deliberately kept away from getting into the detail of the different antigens that might be used because I wanted to talk more about the further down stream issues but obviously those are very important and they are various groups working on finding the best antigen adjunct combinations.

[Applause]

VINCENT TITANJI, Ph.D.: I think you already did it and guess what I was going to ask us to do to thank Brian for this all-embracing, very clear and very stimulating lecture. Let's thank him once more.

[Applause]

We have now come to the end of this session and the next chairpersons may take over.

ABDOULAYE DJIMDE, Pharm.D.: Good morning once again and welcome to the last plenary of the Fourth MIM Conference 2005, the last but surely not the least. While I am waiting for waxing to come the treatment, the anti-malaria treatment remains one of the key [inaudible] fights against malaria. So, the plenary will be focusing on clinical application and drugs. The keynote lecture will be given by Dr. Mutabingwa from Gates Malaria Partnership in Muheza, Tanzania. He is currently the coordinator of the Amani Med, the network, and

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the East African network for malaria treatment. It is the first network for malaria treatment in Africa. So I believe he is the best person to talk of drugs. The Gates Malaria Treatment Partnership commissioned to [inaudible] best malaria treatment but in assistant to the needy. So please you have the floor.

MUTABINWA, M.D., M.Sc. Ph.D.: The chairman colleagues and ladies and gentlemen. I would like to start by expressing my sincere [inaudible] to the mean secretariat for inviting to the Fourth MIM Congress but also I would like to thank the Gates Malaria Partnership for sponsoring my participation to this congress. Last but not least I think I need to thank you all, all have come to listen and I think you have postponed you are to break. According to the program, you will not get— I am supposed to talk on access issues. But being the last speaker, I think I face some difficulties by the fact that since Monday to today access issues have been discussed at length. And last night I was thinking what I was at any use just to continue talking access issues. So overnight, I decided to change the topic and my talk is challenges to malaria treatment in Africa and opportunities that are there.

In taking you through this topic, I have to start from bottom by highlighting the treatment objectives. And once I get there then it will lead me into what are the

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treatments are apparently being used and the challenges facing those treatments. There are or two [inaudible] and I will dwell on how to optimize them and I will end by your concluding remarks.

In terms of treatment objectives, we are now that we normally treat either uncomplicated or confected malaria. And these have different treatment objectives. For uncomplicated malaria we are very much interested in curing the infection as early as possible and prevent it's progression to the severe disease and touches the bases of prone to diagnosis and treatment. Then as you treat, you don't want once you start treatment, your patient despite the treatment you give still progresses to a severe morbidity. All guess additional morbidity from treatment failures. Again, there is some element of the community aspect of the treatment that we use. They could be good to the patient but they should not cause them as does to the augmented.

What do I mean? Here I am addressing the issue of using malaria drugs that end up raising the [inaudible] in your patients. Those ones with active public transmission. I am talking of the drugs, which you give. They don't cure the infection, they select for resistance strands and these are eventually are going to end up with the intermediate size of resistance strands and they were perfect for the transmission

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of resistances strands. In such case, you will be promoting resistance but ideally, the intention of treatment is to prevent emergence and spread of resistance.

With the severe malaria, something was talked on this on Thursday but the major objective here is to save live. You are dealing with life or death. And you would agree with me and also consensus you don't have to think of whether ACTs are safe or not. I am talking in terms of treating pregnant mother. And if pregnant mother comes with a severe disease you don't have any malaria drugs, I think you are justified to use ACTs at whatever gestation age.

Now as I already mentioned, as it was mentioned, earlier before by many other speakers, I think and malaria drug resistance is our major challenger in provision of adequate and effective treatment. Anti-malaria drug resistance unfortunately is affecting the anti-malarial drugs that are less expensive for Africa. This is an additional challenge and difficult. These drugs you know include artesunate and sulfadoxine-pyrimethamine. There is anti-malarial drug resistant artemether but enough amodiaquine is not all that much used. But as you know even without using mefloquine in research studies in Africa is already indicated mefloquine resistance.

I will quickly show you these maps from projected by

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Tom Sequoir Eti Lumas [misspelled?] and I guess WHO the same maps. And just to impress upon you that currently chloroquine, SP, mefloquine. Chloroquine and sulfadoxine-pyrimethamine more in Africa, mefloquine in Southeast Asia but as I said earlier we have also in vitro mefloquine resistance. But based on these maps there is something I wanted to discuss with regard to challenges in treating malaria. Those who are present at Thomas Sequoir's presentation yesterday when he was listing the recommended ACTs they were four but below he talked of a combination of artesunate and SP that is going to be your as an intervention therapy provided parasites are highly sensitive to both drugs. And that is the catch. Better recommendation was made four years ago or three years ago, 2001 now is 2005, by then I think we had not been faced with a higher level and degree of both sulfadoxine-pyrimethamine and artesunate. But now we have in that area and as you might see on the first test, [inaudible] seen some horrible presentation that our countries, which are already testing or even deploying the nation of SP amodiaquine. My question is yes, their deploy may be they started deploying when they were malarial resistance to this drugs were still low. And when the physician continue to deploy these drugs two to three years from now we are not sure their resistance isn't level to both

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drugs will be very high and by definition then they are not suppose to be combined in terms of offering treatment to a malaria patient. This is something we need to think about, discuss and come up with a resolution.

Now the consequences of resistance are quite fair. The major one is you treat for parasite activity persists and this for [inaudible] ending with either chronic disabilities anemia or the same parasite activity may present with another phaco episode. The chronic parasite activity would end up with chronic anemia. And once as I said area you keep wondering about parasite activity there is a high chance these parasites changing into gametocytes and with all of these, the improper transmission you perpetrate chronic malaria associated diseases in the cells you are [inaudible] malaria degraded morbidity. Those who have read books knows a peer preview you are not at it said since their resistance are malaria morbidity, mortality as raised two to six folds. And that is my interpretation of why malaria drug this doesn't mix. This having been said then we need to find measures of slowing that [inaudible] can spread over a malaria drug resistance.

I have listed three approaches where we can manage to reduce the millions and spread the malaria drug resistance. Number one is always said but it is difficult to implement

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especially in African setting. We should avoid wide spread instrument use of anti-malarials. I agree but how. In this session, there has been presentation on home-based management. In appropriate to introduce [inaudible] home based management is going to be a good source of indiscriminate use of anti-malarials. Therefore the perpetration of drug resistance. The other approach is as we have lead area is to use drugs in combination. And the concept of combination therapy is that each drug protects one another and it delays the millions of anti-malarial drug resistance to a drug. The other way of ensuring or lowering malaria is to ensure you use an effective [inaudible] that you look out of the possible parasites that many linger around in the secretion and tune to mutating to resistant strands.

Now from now then I am going to concentrate on the issue of combination drug. I don't need to go into the details of the concept of basic combination therapy; I think Tom Sequor did a good job yesterday. All I need to verge on further is why ACTs and now any other combinations as of now. One we are not at the ACTs are rapid acting so they rapidly rid of parasites and rate to rapid resolution of the symptoms. Basically, they act on species of malaria but a later to say this is general. Ideally, they act on every

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stage of all species of malaria. So now is where [inaudible] does not come in. ACTs are not as highly efficacious as on late stages but they are highly efficacious on other stages so there is need even with ACTs to ensure who approach diagnosis so that you catch the malaria clinical episode when the [inaudible] of the ACTs act in their early stages and in that much later stages. There is this notion of observed as are indicated later that artemisinin or ACTs have the potential to reduce the [inaudible]. How this is implied in terms of transmission is still a question especially in the high [inaudible] of transmission.

Nothing has advantages that cannot present with some trouble. So, ACTs have some troubles. One I am going to do on this is cost; the other is a short shelf life. We will—all the time we use the term we give SP with a long shelf life. You can order vial of SP currently and use them for the next four or five years but it is not the same with ACTs. Their shelf life is short so you need to plan appropriately. Get the right CCs of drug each country need within [inaudible] material and then you prepared to order the real order. This is not a simple thing as in the African cities. So, that is another problem.

The next, the third trouble is the short half-life of the artemisinin within the current depression. I have said is

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about an advantage and a disadvantage. It is an advantage in a sense that it gets in, gets out quickly so no chance of parasites that remain to get to tuned to mutate in to becoming resistant. But it is a definite advantage in the sense that you will need frequent dosing schedules to reach up the market objective levels of dead parasite. You all know that with ACTs hat [inaudible] that you need to give it some frequently. This is a not an easy thing in African setting especially to the late oppression in the communities. So that is something maybe the drug companies want to consider. We have discussed it many times but there are now easy solution to this.

The recommended ACTs, there are four. I think over the four I will in quantum later but I need to draw your attention on what I already said. There are some combinations recommended in 2001 that incorporate drugs like amodiaquine and as I said earlier, 2001 sensitivity of malaria parasites to amodiaquine was better. It can't be compared to 2005. And as we go along, I am sure the sensitivity changes to the worse. Then the question is at this combination where did I combine into drug which we know there is a resistance and is increasing going to be of any use in the near future. There are companies working you on a commission of amodiaquine and artesunate. So you have seen the outside data but if we don't

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do this combination very first [inaudible] it will render B of no use if it is brought up to two or three years later when amodiaquine resistance is so full fledged and then the combination is of little use.

Now I have said ACTs viewed in the publications they said they are good drugs. I agree. But [inaudible] to see where in Africa these studies have been done, [inaudible] well I am taking example of KwaZulu-Natal. It was projected by Brown where combination of amodiaquine with AS managed to reduce the malaria bug by 90 percent. That was good and we are once [inaudible] but the question is how representative, how [inaudible] nutrition in KwaZulu-Natal to the rest of the malaria epidemic countries. We are now economically—South Africa is well off. It can't be compared with other countries. We are known very well the infrastructure and the [inaudible] distribution system of South Africa health ministry is far better compared to most of the other malaria epidemic countries south of the Sahara.

These are key important elements which need to be in place in order to make your ACT work optimally but as I stand now I am quite sure most of the southern infrastructures are not efficient. They are very distribution—there are people in the communities so—we need to talk of ACTs but at the same time make sure we address the infrastructure and whoever is

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funding the promote of ACTs I would strongly recommend that money should be allocated at improving the first infrastructure especially addressing distribution of the drugs. Otherwise—then there is Sumbul Tanzania. Which is toward [inaudible] amodiaquine with—another study where they compared amodiaquine/ SP they came up with comparable data from day eight QRAs of parasites brace but the difference is that for chloroquine most of the parasite activity they got were new infections but amodiaquine/SP these were reoccurrences. So although you can argue that let us continue to use amodiaquine/SP because it is again comparable results with the artesunate you should realize that parasite activity that you are getting and amodiaquine/SP is just a—and just as I said earlier this representatives are not good especially if you have ordered or selected for resistant strength because most of them are likely to end up tending in the middle size which are actually containing resistance strands and you would be prorogating the problem. For Tanariya again we said chloroquine was effective but the infection rates were very high. This is a challenge and a big challenge to those who are dealing with the punishes, national malaria control programs, and the people in the minister of health because you are going to give a message that we have grievous with what this one [inaudible] Artekin does it create

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clinical episode but as long as the infection rate is high these children are going come up with frequent reinfections, chronic parasite activity, chronic anemia. These infections may end up in clinical episodes so I don't know what will these people in the community think of you. You said you had a wonder drug but they still see the children are frequently being infected all frequent, frequently getting sick. So it is a big challenge and the best way out of this is actually to make sure the communities understands what is going on. It is not as SP, [inaudible] suppressor that presents for a longer period. It is artekin, amodiaquine doing its job getting out. Once it gets out you have risk of new infection. As long as the communities understands this then you will be welcomed. If they don't then they will think you are treating them and they wont abide by the policy you are just trying to do. That is how I think.

Regarding co-acton [misspelled?] the same drug I am not sure how many of you have read. There are some papers coming out showing some tolerance to co-acton it self and we think there might be room for further resistance coming up. I don't know when it is going to [inaudible] isn't here. He might talk more on that. And since I come here Monday, I have discussed it with a number of other people. I am told there is a similar finding I think is it Columbia or-go into the

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other issues of funding and the politics of funding and funding agencies. I thank you all for being patient despite the black out. Thanks very much.

VINCENT TITANJI, Ph.D.: On your behalf I want to thank Dr. Mutabingwa having the courage to continue despite the [inaudible] used to send us. What I would like to do, I would like maybe to sit at contents of this presentation who is [inaudible] thought that is no problem. You take just one question is that a question just one question, please.

MALE SPEAKER: Yeah. Thank you. Dr. Mutabingwa brought to you a nice presentation. I guess I was more impressed on signing the lock up, a new drug, which was developed a few years ago to treat malaria in Africa. What is the future of that drug? I don't see you talk about it at all. Thank you.

THEONEST MUTABINWA, M.D., M.Sc. Ph.D.: Thank you. That is a good question. And I wasn't in despite the blackout I would never have mentioned about that drug. The reason yes I agree Lapdap [misspelled?] is a drug now resisted in UK and in about I would say fifteen countries in Africa. But it is facing a bit of a problem and it is the problem arise around that Lapdap is not a conventional therapy yet you are talking of combination therapies. But then there air force and I am sure they are sitting on going to produce of combination of Lapdap plus artemisinin. As you have seen in the [inaudible]

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sessions they are presentations or Lapdap dosing schedules in quite a view but despite all of these efforts I am still not sure of the Lapdap story because recently I was at a meeting in Euro Africa and there is a green book on Lapdap published by the World Health Organization and this one is sent to the news or what have and when I read the executive summary of that book, actually I don't know where we are heading with Lapdap because the content of the executive summary you presented to the person makers in the minister of health and a year later, you go with your package to say I am recommending Lapdap, I think this person make a-won't listen to you. So there are issues and the issues in there they are political issues and I was told that the WHO meeting that they have gone back to GSK, GSK is readdressing the amodiaquine issues, they will come up with maybe no [inaudible] and recommendation on the use of Lapdap and that is why I purposely didn't want to talk of Lapdap as of now.

VINCENT TITANJI, Ph.D.: I think we are going to conclude and the discussion may continue in the hall because [inaudible] to open drug malaria. I would conclude it as subject to mediation. One of the limitations to the deployment of ACTs is the cost. Our elite grouping is on HIV. We are able to push the manufacture to redo the cross. I don't know why malaria because of the [inaudible] of drugs

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should remain high. So, I think meditated on it until next
year. Thank you to all of you.

[Applause]

[END RECORDING]