

**Fourth MIM Pan-African Malaria Conference  
Yaounde, Cameroon  
Drug Resistance  
November 16, 2005**

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**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** I Am Robert Guiguemde. I am from [misspelled?]. I am your coordinator of West African Network 2 for monitoring malaria treatment. My co-chair is Dr. Fred Kironde from Uganda Africa University. Before we start our conversation, there is notification of the program. Kuran [misspelled?] will be on the program. It will be differed against Trivoski [misspelled?] and for tomorrow the current controversy will be on mosquitoes, which is a change. Right, the next speaker is Professor Wilfred Mbacham with surveillance in Africa. Now, you have the floor.

**WILFRED MBACHAM, Ph.D.:** Oh, thank you Professor Guiguemde for this opportunity. I am going to talk a little bit about drug resistance surveillance in Africa. And I will be bringing to you basically, the different methods that are used in this drug surveillance and the challenges and problems and difficulties that are being viewed in these kinds of studies.

In my first slide, I first of all start by saying that there are many factors that affect drug resistance and these tend to be clinical social issues. The first of them is the bioavailability of the drug, which is greatly influenced by nutrition. But also increasingly and which is

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being proven, by the admittance [misspelled?]. We know of populations that live in synchronicity that have different responses to several medications and that is increasingly the case also with malaria. We know that they also say that tomorrow amount of drugs in certain medications that are sold in the black market and even in people. Also we show the willingness to take these medications and we're not sure if they are taking the right amount of drugs in there and there's still a lot about the right amount of drugs, which ends up generating and propagating the resistance. And that is usually is ascribed it to be [misspelled?] . Human behavior is still something that we need to consider and given the fact that for some of the new medications, or those that are currently on the market, the tendencies for people to take this medications and wants to feel better are doubling the amount of tablets because they think a child or another brother will be ill soon of this disease. Perhaps, propagating resistance because the residual parasites that stay in blood ultimately they have become resistant and those that get propagated. Next slide.

In the next slide I bring to you the different methods that are used in generating the data necessary monitoring resistance across the board. For most of these methods, quite often because of costs constraints, many

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people don't usually apply all of these methods in generating the necessary data. A comprehensive approach is very important and necessary. And the first time it is important for us to know the individual efficacy of the drugs and to follow up. The difficulty has been that many people apply what has recommended by the WHO. Some people will do for 10-day trials, other 28-day trials and we come to be difficult and problematic to compare. For the individual aspect, the absence of entering in the database, [misspelled?] many human factors help determines exactly the parasites potential to become extremely resistant, in individual trials, quite a few of range of [misspelled?] to know exactly the extent of which the parasites have the potential to be resistant. The use on their use, doesn't provide data, so quite often [misspelled?] have been developed elsewhere that are many meaningful for the researcher. For example, the reverse assays [misspelled?] in which the use of antihistaminic medication to try to reverse the resistances to a range of anti-malarias. That becomes more really for the individual assays. Molecular markers have seen the light of day. These are still being developed and categorized but they are in the range of these mutations and specific genes that are being ascribed to be so short to the resistance that we see. The other aspect, or the other problem for them and is very

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important for them to collect is the level of drugs in the blood of the patient. Because this is determined as to the right concentration was available to make it resistant. Now, a combination of these four parameters actually should provide the complete data on civilians against resistance in Africa.

In the next slide, it's a must that for all data that is generated, this must be locked into a database. Databases have been developed, for example, that of the Anti-malaria Resistant Network, the [misspelled?], which actually is the best control of information. But it takes quite an investment to develop such a database and to have it working. And if such a database is available, then you no longer keep it within one group, we want a range of other groups to share it. Which makes the point that the fact that setiment works with less function and this message must exist, must have this database?

For the network [misspelled?] to work to provide the necessary information, it is important that we have the funding, and that the funding is sustained a very long period to generate data for many, many years. This is also important that such networks have good leadership and that all of us in the network are trusted and not diverted in contributing the

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data. Otherwise, any patient who comes as the weak link determines the strength of the group.

It's also important as we begin to generate this data that the methods, which these data are generated, are comparable, otherwise it wouldn't make sense comparing apples and grapes. Next slide.

I bring to you some of the variations within Africa that have been observed in the year 2004. And these bars are indicating the [misspelled?] from the regions are that here are presented between the East, Coastal, West and the South of Africa. With comparing the [misspelled?] situation and the different anti-malaria drugs that are described.

First of all, we notice that for chloroquine for example, there is very high resistance in the East through the Central and [misspelled?] in the West. If you compare that against the situation in Asia, then you are to think as we all know that resistance to chloroquine actually did generate from Southeast Asia and spread to the East Coast of Africa in the 1980s and subsequently took on the entire continent by the late 1990s.

And the most line for falciparum resistance, you notice that the situation is a little complex and we need to understand whether the situation in Central Africa means anything in this symposium. You notice that in certain

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areas, you just don't get any resistance to SP, whereas in other places you get extremely high resistances to SP. By using studies, which I'm sure will find on some of the posters here, that [misspelled?] populations of parasites that carry resistances to SP that are in circulation. We are going to see more discussion and to separate presentations come up.

In the next slide, I tried to represent here one of the first line of anti-malarias, right on this slide for a colleague of mine. And to demonstrate that just two years ago, we found that there isn't very much of a [misspelled?]. And we found quite a few countries still using choloroquine until lately and in the next slide, it becomes almost a mosaic with [misspelled?] in to anti-malaria combinations. Most countries using the SP, no [misspelled?] on falciparum and the others were using [misspelled?]. This situation is a very complex situation and I think this is a very simplistic view. If we have to represent this in terms of the resistance patterns, I will want to present the example of the great expanse of the country called Sudan. And you see between the North and South, that to put up a national policy would require that everybody be subjected to the same kind of conclusion. Where with us, have had to see if you're in between the [misspelled?] of that country, you would find

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that there are different resistance patterns which one needs to determine, which caused for them an audit an increase in the necessity to, ready to [misspelled?] the country and determine to treat East and West, North and South and where the resistances are. Then be ready to put out some kind of regional mapping of this resistance patterns.

The in the next slide, I try to bring you the [misspelled?] that you seek. Can you continue to scroll down? That currently exists which can help, through this monitoring effectively as we continue to have a better understanding of the disease and infections. These range of mutations and different genes are currently being used, and you will find quite a few articles that have been an abstract. That has been published on the abstracts of this meeting, which describes these mutations. And this fact that [misspelled?] increase of [misspelled?] numbers to [misspelled?] as well as [misspelled?] mutations. And this will form the basis of determining exactly what the situation is as we have a better understanding of how these play into the drug resistance situation.

I bring you the situation of Cameroon, just to show you some of the harder elements that exist and the difficulties of having to monitor the resistance. It is found that in the South we find the bars are much more than

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those in the North are. And these are data from the meetings that demonstrate that chloroquine is of extreme high resistance in the South than it is in the North. It is of high resistance in the West than it is in the East. Now this is a picture of chloroquine. That if you look at the white bar, the white bar represents the resistance to mefloquine, and you find as well as resistance to mefloquine and enough that it is in the South. These are not in pursuit for the drug [misspelled?] or this [misspelled?] the condition of resistance is to this as to malaria drugs.

And the next slide. All I try to bring to you as well, as the fact that looking at the far regions, the provinces [misspelled?] in different regions of the country. You find that for the [misspelled?] of mutation, you find in different places within the country that there is a very sharp reduction in the province of this particular marker. It has not for chloroquine-resistance; it's almost part of it. Both are 80 percent. We have correlated that it suggests or demonstrates that the [misspelled?] drug mutation equally has way higher than 90 percent. Evidence also that the [misspelled?] mutation one way has gone past 85 percent among these time within a period of four years.

Next slide. I bring to you right away the data. There are DH prototype [misspelled?] in use of clinical study

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that was ended this past June 2005, which shows you exactly the different type of parasite populations that do exist, and you notice that the entity of the prototype is just more in the North than it is in the South. For us the SKT [misspelled?] exists more in the South than it is in the North. Next slide.

If you combine that with the adequate clinical area of response, then you will see there that there is an [misspelling?]proportion [misspelled?] relationship between the acetylcholinesterase response and the presence of the SQT [misspelled?] mutation, which is represented in green. The acetylcholinesterase response is being presented in blue.

And the next slide. To take a message from that trial basically hinges on the fact that the resistance is less, as we know, as this has been spreading from East Africa to West Africa and there's more evidence as you will see in the talks that are further. And the tracking relationships need to be encompassing of all the parameters and measured once against the most we sustain and propagated needed for this data to make meaningful in policy changes. The current data as you will see, suggests that it stresses for an eco-type as [misspelled?] policy as opposed to a national policy. I'm told those 30 minutes ago that this is possible if you de-centralize the healthcare system.

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In all, drug resistant studies [misspelled?] and determine their resistance, must be an integral part of the drug resistance surveillance, otherwise the data will not be meaningful for policy makers if they do not know exactly what drug the resistance is and the areas where they have found to be no longer effective. Thank you and I will take some questions.

[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Thank you very much for this review for the African situation with drug resistance. Dr. Mbacham, I have about a few questions for about five minutes.

**DR. WILFRED MBACHAM:** Yes sir.

**MALE SPEAKER:** [misspelled?] pattern of resistance, is this coming to East Africa and West Africa? I am wondering one of the major contributions to resistance [misspelled?] is a practice of certain litigation in the adequate treatment that goes with that. Thereby, developing early since resistance to pick this pattern to the compartment of [misspelled?], that's one question. The second question is this; the [misspelled?] data comes to the drug because we all know that the policies come from [misspelled?] we all know that. The accurate [misspelled?] obedience that goes with the drug play a part and if this

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shows it is very advanced in producing generic folks [misspelled?] parasites for most of it, the firms and the A countries that were producing them. So I wonder if they would depend on the quality of this generic [misspelled?] that might be related to the development of resistance. Thank you.

**MALE SPEAKER:** [misspelled?] Second question.

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Dr. Mbacham might be able to answer that one then.

**DR. WILFRED MBACHAM:** As to the first question, the area of drug resistance relatively due to the habits of the people. It's hard to pinpoint only one reason why this resistance developed. It's probably that it could be the combination of many factors that ultimately influenced this plague of resistance. As you know, resistance basically began just came from Southeast Asia and also from another focus in Latin America, in Indonesia. The resistance that we find in Africa basically came from Southeast Asia and the propagation that resistance parasites is also apparent as a result of the alleles [misspelled?] if you take away [misspelled?] and you do have complete the prescription and still you will pass on the resistance, you feel that they're combined with the fact that in certain areas there are very high transmission. You get more in breeding and cross-

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mutation of the species makes more resistances as grow populations when they are together. They increase the resistance and for you [misspelled?]. At the same time, we all know that the medications that are sold, they have several [misspelled?] quantities. That they show itself, even we you take the complete prescription, and to complete the question. In complete of the next question, we are not providing the message [misspelled?] right amount of [misspelled?]. The [misspelled?] second question about the presence of evidence in [misspelled?], these are the difference in generic drugs. I cannot make a statement. I did not know how many these additives, in the absence of the additives play in drug resistance. There are the ones that you know are cheap and it's meant to help the poor people and so we gave them.

**MALE SPEAKER:** I have another question for [misspelled?]. Another question.

**MALE SPEAKER:** Thank you properly for that [misspelled?]. I am particular in the area of molecular markers. You may feel about these markers and I think you do because it is a process of development. How many of these markers are now intend to use as a particular in play for malaria drug development?

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**WILFRED MBACHAM, Ph.D.:** Well, they are calling most of them that they are actually being investigated. If you notice there are these posters for the different genes; DHPSS, DHFRs, [misspelled?] the other one these are certainly your classic mutations that have been pursued for many years.

The voice of [misspelled?] was that in addition to these poor mutations, people are looking at the hosting around these particular mutations and finally you have that memory [misspelled?] the [misspelled?] has been affected by mutations and we know turn to describe the habitats as a combination of mutation and generally at the point mutations. We are [misspelled?] know that they are mutations that are actively being pursued. There are other abstracts here that also point to mutations, on a new gene on [misspelled?] for example that [misspelled?] or me and resistance and looking at the plasma in [misspelled?] found so they might begin exchanger. That is just recently of three years described. We also tried to describe mutations within the PFATP6 gene as related to that whole [misspelled?]. And these are rules [misspelled?] have come and I think that people will be making more combinations of different genes to define the resistance pattern to [misspelled?] and to go around medications and there's really no prescription and the accent

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of which these can be used in surveillance of the evolution of drug resistance.

[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** And thanks again to Dr. Mbacham. I will next announce the next speaker; this will be presented by Jaishree Raman.

**JAISHREE RAMAN:** Thank you. Could I have next slide, please. The NSDI will be special development initiative with a trilateral communication between Swaziland, [misspelled?] and Mozambique and in improving the Lubombo, which is an area grey into an economic area. But the greater problem found in that area was that there was a high incidence of malaria. Next slide, please.

And you have a little of that in Swaziland and [misspelled?] if you look at the prevalence at the incidence, it was about one percent. Where when you look at Mozambique and the Lubombo area, it was about 85 percent, which made these two governments realize that they if they were going to do anything to make these economics viable, they have to do something about the [misspelled?] and they wanted to establish a malaria-control program. And thanks to some funding from the Global Fund that was established. Next slide, please.

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What happened was they decided that the control program would be at Mozambique from a southern most part of Mozambique and the progress northwards. And this was mounted in stages. The first one started in 1999 and 2000 and so once there, I am able to discuss today. And has progressed up to 17 in 2003 and now we have a whole area of over 100,000 squares [misspelled?] and trying to enhance this malaria program. The Malaria Control Program consists of two parts. The first one being the vector control and it was with IRS and they used DDT to sterilize the hut, which was very effective, and at last count the vector's [misspelled?] down to about 10 percent. The ceiling [misspelled?] was realized that just having a vector opponent wasn't good enough for a vector control program, so we had to also control the parasite. Next slide, please.

And so you had to have two parts of it. One was definitive diagnosis, that was using rapid tests to diagnose for malaria definitely, and the second leaded into an effective drug. And we decided to move to AZTs. And now within the region because there were different levels of resistance to the normal mono therapies, the combination therapies were chosen to suit the region. Kwa-Zulu-Natal lifted to co-op in 2001 because they had very high resistance to both chloroquine and SP, whereas in Bumalunda

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[misspelled?], which is another province in South Africa and Swaziland's, one moved to [misspelled?] SP combination. But this phased a little bit of problem with us when we were monitoring this, because we knew Kwa-Zulu-Natal when we changed to [misspelled?] had a very, very high level of SP resistance. We know this SP resistance rises very quickly so we had to monitor the level of the molecular markers to give us an indication of whether resistance was developing or not. So what we did, we do annual cross-sectional surveys of children between the age of 2 and 15, and collect the blood spots on, positive samples on [misspelled?] because they were brought back to the lab and we look molecular markers. Next slide, please.

For SP and we look at the most common ones, the three for the DFR gene and the two for DHPS. Next slide, please.

If you look at the DFR gene is 1999, which was our baseline year, it was about 50 percent. And as you can see, over the consequent years it has increased and by 2005 almost every sample that we look at has the triple mutation. Next slide.

And if you do stops on it, it's obviously significant, if you look at 1999 reference year. The picture's slightly different when you look at the DHPS gene. Next slide, please.

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In 1999, we're sitting at about 21 percent. It peaked in 2001, which corresponded to the SP resistance peak in Kwa-Zulu-Natal dropped very nicely in 2004 and suddenly we saw a raise in 2005, which is a very little bit worrying. Next, please.

Because in 2004 we introduced the combinations therapy. Have a look at the stats; the only increase of any significance was the increase in 2001. The picture, however get a little bit more worrying when you look at the presence of all five mutations. Next slide.

And if you have a look at it, in 1991 we were just about at 15 percent, it peaks in 2001. 2005 we're about the same level that was in the epidemic year of 2001. Next slide.

And it is a significant increase to the baseline year. So, now what does this say? You can go to the next slide. I've just got one conclusion. Next slide, please.

To be honest in my talk, yes the mutations are increasing, very worryingly [misspelled?], the SP, and the presence of all five mutations increasing is really worryingly because this is carried at a time when combination therapies have been introduced. However, to make a statement that is negative or positive is a little bit early because it was introduced at the time when we were doing our field

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collection. So maybe, by the time we have a look at the results next year; they'll be somewhat different but is what is very important to make sure that nothing deleterious happens is that we make sure we have good en vivo and envitra [misspelled?] studies carried on concurrently. Thank you.

[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Thank you very much Dr. Ramon for your presentation on "The First [misspelled?] mutations DHF and DPS in Southern Africa." Dr. Ramon has some four minutes to answer questions.

**MALE SPEAKER:** I am with Harvard/ during that presentation did you have in-vivo data either from 2001 or 2005 to see how the clinical treatment of the combination with pyrimethamine and SP, right?

**JAISHREE RAMAN:** It's more closer in 2004 and it's been very, very effective. Most of the children have recovered within three days, but we did find and we followed the patients for 42 days. We find a lot of re-infections after day 28. We haven't had a chance to analyze the 2005 data yet to see if it maps anything like this.

**MALE SPEAKER:** Do you know if the genotype markers in the patients that failed?

**JAISHREE RAMAN:** Yes.

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**MALE SPEAKER:** And did you see an increase in the presence of the mutations?

**JAISHREE RAMAN:** No, I didn't.

**MALE SPEAKER:** The function of the [misspelled?] it's disavowed its [misspelled?] to kill [misspelled?] that would be debatable.

**JAISHREE RAMAN:** Sorry, I'm sorry I missed your?

**MALE SPEAKER:** I come from Niral [misspelled?] and the militia to kill of [misspelled?] would be regrettable because you have parasites that are triple with [misspelled?] and that's a lot different than the [misspelled?] because we know the mutation of the optimal ones are focused on the [misspelled?] and validate the [misspelled?] But the balance, you really get a [misspelled?] is a bit worrying because I'm trying to understand how this reversal of the mutations have increased over 540? But, at some point we have to expect that we should have maintained a level of focus of 47540. I can [misspelled?] with a reduction?

**JAISHREE RAMAN:** We haven't seen that. We just see it continually increasing so, I'm not quite sure our parasite population is doing something different from what is expected, but we just see the levels of those two markers going up. We just haven't noticed any decrease.

**MALE SPEAKER:** Your data is interesting.

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**JAISHREE RAMAN:** It is interesting but I think in 2001, probably a lot of it had to do with a lot of people moving between Kwa-Zulu-Natal and Mozambique. So they would have rather looked at Mozambique people, we had people that were from South Africa hence there was a major peak in 2001.

**MALE SPEAKER:** How can you tell the vastness of Mozambique? We have a level that of the same of mobility down from the South to the North?

**JAISHREE RAMAN:** Yes, I would have a look at the micro-parasites and they're exactly the same parasite population. Yep?

**MALE SPEAKER:** Can I ask as being alone, pretty much alone, is available [misspelled?] and if this could explain the increase you observed?

**JAISHREE RAMAN:** Falciparum was the first line and SP was theoretically the second line of drug. It was never made officially made as a first line drug. So, I'm not quite sure, really.

**MALE SPEAKER:** Were the reagents for 164 mutation and the?

**JAISHREE RAMAN:** Yes, I have and it's not present at all.

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Thank you very much Dr. Raman.

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[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** The next speaker is Alfredo Mayor.

**ALFREDO MAYOR:** Good afternoon. I'm going to present the results on the "Effect of Intermittent Preventive Treatment from [misspelled?] in Infants from Manhica with Sulphadoxine and Vitamin [misspelled?] on the Prevalence of Malaria Markers for Anti-Malaria Drug Resistance." Next slide, please.

So the objective of this study is to undermine if IPT were selecting parasites starting with [misspelled?] system markers. Next.

The molecular markers we have finalized are more falciparum [misspelled?] resistant transported gene and [misspelled?] resistant, one with are in both in [misspelled?] resistant, the high folate endonuclease and the dihydrofolate synthase in both high sulphadoxine and [misspelled?] resistance. Next slide.

So this is previously information in Manhica District from 2001 and 2003 just to show you that the frequency of quintuple mutants in 2003 was around 20 percent. Next slide, please.

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In-vivo studies in this area have shown in 2002 that adequate clinical response of chloroquine was around 50 percent and for SP was around eight percent. Next slide.

So in epidemiology we have used some specification of the lot of the [misspelled?] of interest and then restriction within fact and science, which allow to categorize the genome types, Y type, mutant or mixed infections meaning both parasites with mutant codon and white type codon. To get information about the haplotypes from these yellow-indexed information we are applying this algorithm. Next, please.

So the [misspelled?] of the study is following one. We have analyzed 181 blood samples on fecal paper from infants enrolled in the IPTI Study, who after receiving SP or the [misspelled?] attended the Manhica Hospital with the carry of clinical malaria. So, it means we are eliciting samples from symptomatic children. Next one, please.

For 1993, these fecal papers were collected these children attending Manhica Hospital with randomly selected 30 percent of this filter paper which was successfully analyzed it once [misspelled?] filter papers. Eight-one corresponding to pyrimethamine recipients and 89 responding to SP recipients. Next one please.

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And of those [misspelled?] was the same in SP and [misspelled?] groups. Most of the children received the [misspelled?]. Next one, please.

Number of explicit infection was the same for the [misspelled?] and the SP group. The mean multiplicity of infection was around two and most of the children had two or more vaccine populations in the [misspelled?]. Next slide, please.

This graphic is showing you the prevalence of the different genotypes of the codons as you can see. Mutations seen the edge and farther and the FCLP are very high. Mutations are more than 90 percent of those numbers. For the SPS and for FM and DR1, the prevalence of mutants are around 60 percent. So to see if there was any difference between SP and [misspelled?] we first, next please, categorized the merozoites as white and as mutant and including the mutant and also the mixed infections. We saw that there was no statistical difference between SP and [misspelled?] and any of the codons. Next, please.

In a second analysis, we analyzed the [misspelled?] of the zenotypes [misspelled?]. Why mix a mutant? And we saw that there was a statistical difference between SP and [misspelled?] 51 and 47. To see it in that direction of that difference with a correct 198 analysis and we saw that the

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difference was in the composition of the mixed infections but not in the proportion of white type of mutant infections. And the election of this association that was mixed genotypes for codon 51 of 437 were more frequent in those children who received SP. Next one, please.

So, from this genotype, we got information about the [misspelled?] and you can see the sequence of quintuple mutants is quite higher than 40 percent. We looked for a difference between SP and [misspelled?] and next slide.

We saw that there was no statistical difference between the treatment group and frequency of the [misspelled?]. Next slide.

So finally, we got to leave out; my people got a [misspelled?] analysis by which this qualitative analysis that compares frequency tables in graphic displays. So we have [misspelled?] in the graphics, 12 percent in the different categories of the variables and we can infer from this graphical presentation the association between these categories. Next slide.

Here we have the [misspelled?] presentation. We can see that that SP and [misspelled?] are showing that don't live in any way, anybody is not really clear about that? We can see one or two an organization of the configures of the genotypes, white type and mixed. And we can see also a

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multiplicity of infection, [misspelled?] which means [misspelled?] different parasite populations in white sample this, [misspelled?] mixed category of that genotypes. Next slide.

Here is the same analysis but just concentrating in the expert's columns and we can see an aggregation of the disfigures of the genotypes. We can see that SP antibodies are approaching the mixed category of the codons. We can see also that with [misspelled?] of infection [misspelled?] is near and speak up everybody. And that placebo and [misspelled?] it means low multiplicity of infection at close together. Next slide.

So this out of conclusions you can have from this study. First, there is no evidence of any [misspelled?] in the prevalence of parasites with drug resistance innovations. It isolates from infants with clinical malaria who have the [misspelled?]. Second, there is a suggestion that SP may increase the propulsion of mixed infections in the codon studied and finally that IPT, I dissecting against a molecular assisted genetic background. Next slide.

So, this is a future work we are trying to do. We would like to invite those samples coming from infants with clinical malaria after one to three months after receiving the last dose of SP and we are planning also to analyze

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examples from children from this IPT study in cross-section of twelve months. And this is the people who participated in this study. Thank you very much.

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Thank you very much Dr. Alfredo Mayor for the presentation and situation in Manhica, Mozambique during the IPI disease study. Dr. Mayor, it's time some three or four questions.

**DR. ALFREDO MAYOR:** Yes, sir in the back.

**MALE SPEAKER:** I have to consent for there's the [misspelled?] PFCRT and PFMDR1 because I don't know what kind of relationship you want to make between these markers and SP?

**DR. ALFREDO MAYOR:** Sorry, I didn't really hear the question. You didn't get it?

**MALE SPEAKER:** I say what kind of relationship do you get between PFCRT, PFMDR1 SP?

**DR. ALFREDO MAYOR:** We would say to use these models just as a control. We supposed that they were not going to be effected by SP. That's the reason we are not [misspelled?] also, are those columns involving those systems to broader [misspelled?]. That is the reason.

**FEMALE SPEAKER:** Perhaps I overlook the part of the bigger study and perhaps the bigger analysis is done yet, but do you see an effect of IPTI in terms of preventing malaria

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because you have such a high background of mutation. Is the intervention actually working? Or are you just seeing the same parasite populations in both sets of patients? I mean, is the intervention treatment actually preventing malaria in those infants?

**DR. ALFREDO MAYOR:** So sorry, I did not understand the question. Can you repeat this?

**FEMALE SPEAKER:** Well, I want part of larger study, but in these patients, in these infants, do you know treatment, SP treatment is having an effect?

**DR. ALFREDO MAYOR:** Yes, this was presented in the study and it's having an effect. It is reducing the clinical symptoms of malaria, yeah. The SP in terms of preventive treatment is working, yeah. I don't know if this [interrupted] I don't see for in-vivo sequencing, I wouldn't have used that, I'm sorry. The last data is from 2003. We have not done any in-vivo sequencing in the study, yeah.

**MALE SPEAKER:** Did you take in account? Did you take in account? Of SP treatment and the child [misspelled?] attack. And there was some children like that at clinical attack up to two to three miles from here is SP had been used earlier. So, is there any of that?

**DR. ALFREDO MAYOR:** Yeah, well I have not considered this yet, but this is the warning of the sort of work we want

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to concentrate in those samples coming from children, one to three months after receiving SP. That is what we are planning to do next. In this study we did not consider this.

**MALE SPEAKER:** Just looks the occasional, perhaps I was the only one that was perfectly clear with your answer, these data come from a child that was actually presented yesterday by Dr. Masenti [misspelled?]. SP has been more applications.

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Thank you very much Dr. Mayor.

[Applause]

Now we will call Dr. Samuel Adjei for his notes on cross-resistance makers between chloroquine and amodiaquine in Ghan. Not yet? Somewhere? Apparently Dr. Adjei isn't here, so we move on to the next paper with Dr. Marie Solange Evehe. Have the floor.

**DR. MARIE SOLANGE EVEHE:** Good afternoon. I will be talking to you about PFRCT based study that we did in order to evaluate the efficiency of chloroquine and the treatment of malaria from ecologically different regions of Cameroon. Next slide, please.

It is well know that change that is involved in the transportation and metabolism of drugs in people of Cameroon can be used as markers of resistance due to the appearance of

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mutation of these genes. In Cameroon chloroquine resistance has been observed as early as the 1980s in a town known as Limbe, which is found in the little known region of the country. And since then chloroquine efficacy has considered to be dropped. In the year 2000 and 2001 it was suggested that PFCRT could be used as a marker of chloroquine resistance. Next slide.

And so the objectives of this study, were first to evaluate the efficacy of chloroquine in four sites in Cameroon and this study in the year 2000 and 2001. And secondly to try and establish a resistance of figure intakes. Next slide.

The study sites as you can see were Nkambe, Dschang, Limbe, and Yaounde. And Yaounde being in the forest region, Limbe in the Southwest up around [misspelled?], Dschang, it's more southern and Nkambe also. Next slide.

For the clinical efficacy of chloroquine, we used only the youngest sample, and the other samples from the towns were used to determine the molecular presence of the molecular markers. And what we did was the we, the study of population where children is six months to 10 years who came to the hospital suffering malaria and after confirmation of the presence of parasites and parasitism and the parents or guardians are accepting that the children should be involved

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in the study. Chloroquine was administered and the 14-day WHO protocol for clinical evolution of malaria and anti-malaria efficacy was used. Once that was done, the parasites were extracted and we analyzed the MSP1 to CG2 and PFCRT. Next slide.

With respect to the therapeutic response, we had for the accurate clinical response, 24.7 percent the accurately and parasitological response to it at 38 percent. Early treatment failure was 12 and met treatment and parasitological failure was 25.7. Next slide.

We then analyzed the molecular markers in this three sites, especially the CG2 marker region and we realized in all the four sites that the dominant allele that was found for this gene was the 570 based allele and children had the highest. It should also be noted that all the samples with the early treatment failure had the same allele; almost six out of eight of them had the 570 bp allele for CG2 [misspelled?]. With respect to the PFCRT we had a lot of the mutant in the town of Nkambe and the mix infections we had were mostly found in Dschang but we still had a high prevalence of the mixed in the other towns except in maybe Nkambe which was low. Next slide.

With the eight samples of the early treatment figure, we then tried to see, we had taken samples, blood samples

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before the treatment that's the zero. And after, that's when we realized the early treatment failure of D3 and you can see that the second column which is apparent that the normal parasites by micro liter of blood. And the last column which shows the parasites found on the day of failure, we realized that there was a drug in the normal parasites, the micro litre of blood, but for some samples we realized that the PSCRT at the beginning we had the resistance and the sensitive as [misspelled?] as after chloroquine treatment and when we realized the failure, the sensitive has disappeared and only the resistant was left. But, for one of the samples Y57, the focal treatment we had, sensitive but other treatment was resistant, which was not detected on the zero popped up. Next slide.

So from the results we had of the presence of mutation and the therapeutic failure are within decided to determine the resistant failure index which is just a ratio of the prevalence of mutation with respect to the therapeutic failure and with Yaounde knowing the values of Yaounde, we have an arrow by 2.3. Using that and computing for all the sites, we found failure that we analyzed to be 38, 35, and 35 for Dschang, Limbe, and Nkambe respectfully. This is true that this has increased even over the years because this, this as I told you is 2001, but several reports have been

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made which show that chloroquine resistant was increasing nationwide. And that's why in Cameroon, the policy makers decided to remove chloroquine as first line drug in malaria treatment. So, in conclusion we can say how mutation frequency at the PSCRT selections six allelic reveals potential resistance to chloroquine and also that a high proportion of D3 failure samples were not real affections, very producing low parasite population and this the conclusion could be drawn from MSP1 and CG2 on making the results which fortunately I didn't present because of time. That said I thank you for your kind attention.

[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Thank you very much Dr. Solange Evehe, so after we had the situation in Mozambique and South Africa now, Dr. Solange Evehe has just described the situation of chloroquine in Cameroon and she's ready to take some of your questions.

**FEMALE SPEAKER:** Have you looked recently at the prevalence of [mis-spelling?]. Do you see any evidence for reduced prevalence of the mutation? With the removal of chloroquine as primary treatment. Have you looked recently at samples from 2004, 2005, do you see any change in prevalence of PFRCRT?

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**DR. MARIE-SOLANGE EVEHE:** I know it is increasing from all the publications but I practically have those and it could be probably because they drug having it removed as a first line drug but actually, we have some work which is on-going on the prevalence of PFCRT Team mutations in Guyana which is in the up north in Yaounde and Limbe. We are still putting those results together. Thank you.

**FEMALE SPEAKER:** Thank you for a very beautiful presentation. I call Dedio [misspelled?] nation, the translation [misspelled?] solving at this seminar had the translation similar and was wondering why you in South those the clinical response that you put in the South, was the thing in the South, also in calculating the genotypes for the other mutants?

**DR. MARIE-SOLANGE EVEHE:** Yeah. We tried to find out what it would look like. It is true that from literature from previous publications, it has been shown the chloroquine resistance was higher in the southern part of the Cameroon than the northern part, which is toward the course, especially around the Yaounde way, it's actually started. But all these studies were not based on molecular markers and so we wanted to see if what was being said. Unfortunately, this study being gone to the end because it was done only for eight or nine days, the reason being that, by the time we

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were getting our results and trying to collect enough data, the ministry of health in our country decided to stop the study based on the nation wide spread of chloroquine resistance. I don't know if I have answered your question.

**FEMALE SPEAKER:** Just trying to find out that it said going to have clinical response [misspelled?] at the molecular [misspelled?] over in [misspelled?]?

**DR. MARIE-SOLANGE EVEHE:** There is. [misspelled?] is the molecular markers in [misspelled?] is the substance in the [misspelled?]. Actually it's all there. We have to merge results, which probably in the next or in the future you will be able to know what we got. Thank you.

**MALE SPEAKER:** Over here, can you hear me?

**DR. MARIE-SOLANGE EVEHE:** Yes.

**TOM WALLACE:** Good. I'm Tom Wallace with the National Institutes of Health. Just a comment is the observation of a recrudescence after a child's been given chloroquine and the recrudescence-finding parasites. Pardon, can you hear me?

**DR. MARIE-SOLANGE EVEHE:** I am a bit slow but I can hear you.

**MALE SPEAKER:** Maybe rock stars do this, right? The observation of a recrudescence after a child's been given chloroquine, and then the observation in that recrudescence

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of parasites carrying a marker, the sensitive license in '76, could indicate one of two things. One, in all of our studies, it's been shown that we found that if the first possibility was that the child just didn't get enough chloroquine in the blood stream. And when we got in and tried to verify that, every time that's turned out to be the case. The other possibility is that there really are resistant parasites in that recrudescence that carry K706, with genetic marker that indicates sensitivity, that has never has been observed in these field studies in Africa. And of the staff that come to stay on the alert for that because if you do confer a case 706 recrudescence or a license [misspelled?] in parasites carrying these wild type markers. If you see that recrudescence in a child who's had adequate chloroquine, then you're looking at a new mechanism of chloroquine resistance in Africa. And that is an astounding finding and it's just a general comment I have. Many of these different studies where there are these rare observations as in your table of recrudescence of the sensitive marker.

**DR. MARIE-SOLANGE EVEHE:** Okay, thank you.

**MALE SPEAKER:** I would like to see the liaison between the indexes; I mean the FI and what upon in terms of failures in these slides?

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**DR. MARIE-SOLANGE EVEHE:** It gets in?

**MALE SPEAKER:** Between the genotype of all  
[misspelled?] and the treatment failures in these slides?

**DR. MARIE-SOLANGE EVEHE:** NO, no we did not.

**MALE SPEAKER:** It could of interest if you could  
find it, to be able to credit the resistance [misspelled?]  
the resistance. So, out of these slides you didn't try to  
see these relations?

**DR. MARIE-SOLANGE EVEHE:** Actually, if you were  
allowed to take this study to the end, probably it would have  
carried that out. They set towns that are very far Yaounde  
and so we needed to organize ourselves according to plan. We  
could not win, once the government sees no more choloroquine  
as first line treatment and possibly some other studies that  
were carried out in Yaounde by all the scientists, we could  
not continue. But I take note of that, probably that will be  
taken to consideration in the future. Okay, thank you.

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** There are no other  
questions, thank you Dr. Solange.

[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** And so there are  
no more questions for Dr. Solange. No, so we go to the last  
paper that is presented by Ernest Tambo.

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**ERNEST TAMBO:** Good afternoon, ladies, and gentleman. While that is the topic that we have, we will be discussing in a few 10 minutes. Next slide.

While we have heard about drug resistance from Dr. Mbacham and Odam, [misspelled?] co-presenter, resistance is increasing and there is a group of children under the age of five in our government and no immune traveler visiting in Africa, Asia and Oyo and the [misspelled?]. Next slide.

While we talk mainly on SP resistance in Nigeria and this one we show you the general resistance rate in Nigeria. It is also to be commented that by 1990 there was no trace of drug resistance in Nigeria. For credit this was due to lack of policy. The rate increased to about 24 percent by 1997 and presently the resistance by [misspelled?], two dozen and four go up about 27 percent. Next slide.

Well, for so much about the different causes of drug resistance and [misspelled?] one of the resistances is [misspelled?] on the two known enzymes, DHFR and DHPS, as we have every indication now we know are rampant in Africa. Next slide.

The long-standing rule of molecular biology is to look for molecular biology which that can adequately predict the [misspelled?] outcome and possibly be used as a policy in various countries in Africa. Next slide.

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While we up to now, there is a determinant of molecular markers as being resistant is still not clear nor do we know the real cause of, action of, function of, as well the integrities factors of parasites and still a challenge to Africa scientists. Next slide.

While this all to go to the study, we are trying to look at a different set of mutation that will [misspelled?] predicted the outcome and to look at the relationship between the parasite and the host immunity and the response. And to see what establishes a simple malaria market, to predict the treatment failure to SP. Next slide.

Well, the study was carried out for malaria research at the Institute of Advanced Medical Research and Training, at the University of Ibadan and it took to cover our receipt by the Joint UI/UCH of Ibadan Research Hospital. While it was also approved by the Harvard School of Public Health, it took down on [misspelled?] indigent patient between six months and twelve years equipped with this study with falciparum and [misspelled?] of uncomplicated malaria. Next.

The patient was treated with the single dose of oral SP. These are in transferred in the gram of kg body weight of sulphadoxine compound. They were follow-ups for the first seven days and later by the days of 14, 21, and 28. The outcome was based on the WHO, 1996. What we found with

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mutation we extracted DNA from this patient using the chelex method and when I added the Nested I application and full of [misspelled?]. And the primary application conditions were these on doing described as seen in 1998. Next.

Well, we also want to add to the flagship between the resistance and amplication on those preferred treatment. And we mainly used the MSP2 to be able to retrace the different relationships between the two set of patients, those that effect treatment. And also I used that to evaluate the complexity of the parasite [gap in audio] FC27 and the RC37. Next slide.

Well from this I told you, you can observe most of the patients were used were mainly children from the age of five from you can see the mean 4.19. And when the children were aged less than five, we have about more than 25 percent of the patient and all of this in the study were many children. And if you can see the area in red, we had geometric mean of about 25,963 parasite count in the blood. And you realize that more than 20 percent enrolled in this study had a parasitism of more than 1,100 parasites per microlitre of blood. That is an indication that Nigeria, Harare, and Dominique [misspelled?] is aware where malaria is. It is very prevalent. Next slide.

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Well, this is the treatment outcome showing you the distribution of how the treatment outcome. We have a purely [misspelled?] percent and a failure rate of about 27 percent. Next slide.

While looking at the prevalence of the mutation at enrollment, this was [misspelled?] in all the 109 [misspelled?]. You [misspelled?] codon one, it, or the genomes that we have was the prevalent and it was 23 percent of the patients. And you have a cross-section on all of that was and you have the triple mutation in the GSFR. Way up level 42 percent of enrollment and if you will permit, I am going to up to 25 percent at enrollment. Next slide.

Well, this is a pre- and post-treatment analysis of this sample and in green you have the native man and in blue you have the [misspelled?] man in all the various with that. And while we realized that as only seen at codon 51 and a gene at codon 50 at GHFR where the prime mutation most infected by the drug and we all know that SP has a limited action of the selective visual in recommended by different malaria scientists. Next slide.

While this show up again the mix for the morphisms for DHFR and DHPS and you can look and see that we have the prevalence, post, and pre and pre and post in green you have the post the pre and in blue you have the post. Realize that

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at codon 51 and 59 you have the prevalence of those that [misspelled?] edition in the DHFR I presented and it's post-treatment, which was not similar due to the circumstance, and this genome was [misspelled?] and reported that SP will increase the prevalence of mixing fiction. And in this study, [misspelled?] to that one because you at last similarly at DHFR at 540, we have a high prevalence at [misspelled?] after the treatment a lower percentage. Next slide.

By this show was just an indication of argumentation those in [misspelled?] patient and [misspelled?] patient. You can see this shows the volume each of this except the GHFR was put on one bullet, which was no significant, as we see the treatment failure. Most of this, each, and every of this GHFE and GHFR was significantly associated with treatment failure [misspelled?]. And where you put down to the treatment mutation you realize that the treatment was done. 10859 was significant as triple mutated failure. What this was more [misspelled?] mutation less than five because the patients were both five years old. The triple mutation was not significantly as you in treatment failure, as reported in all that previously was reported in Africa. Similarly, the genome [misspelled?] you can see the cure and cure for [misspelled?] was in 14 percent and the

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[misspelled?] is 8 percent. This quintuple mutant of triple DHFR and double DHPS was significantly associated with treatment failure. Next slide.

Well, this one a cross-section of the different sets of polymorphism, which would be associated with treatment failure. And from this you are going to realize that as far as [misspelled?] codon from one or eight cannot be used as a significant marker for predicting of treatment failure of SP. As we go up, we realize that the treatment mutant, GSFR was significantly associated with treatment failure as I said earlier and usually try to strategize in each group. I will learn to [misspelled?] realize that the particular mutant there was a very low proportion of patients who actually failed treatment. That was pure, because in book we [misspelled?] out five and above five. All the patients that have the mutation were failed in treatment with SP. Well, this has a different implication because when we look, I did these, we can have related to different [misspelled?] that happened [misspelled?] in Africa to have a clear cut because all of what I propose that the single mutation in THFR maybe like as you have seen at codon 51 or [misspelled?] codon 59. Coupled with maybe the [misspelled?] at codon 540 will be used as a single model for many SP resistance. But this

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study shows it may be difficult to use this marker or the 2 marker to be able to classify such things. Next slide.

What this shows is a percentage of seven-selected [misspelled?] at SP. If in our study earlier you realized that codon 51 of the GHFR and 59 or the GFPS we have a very high proportion of patients that have the selected profile. The parasite was highly selective by the drug. Next slide.

When the impact of age using the age-satisfied model, realize that using the age specified that is patient less than five and patient above five. The presence of quintuple mutants was significantly predictive of treatment failure in this age group. That is patient less than five and patient above five years old. I will note about the immunity developed by this patient over eight. So, from this same thing we can conclude that predicting about immunity may not have the significance to play in the community and the commission of polymorphism. We know how the significant this is to play in the planning of parasite. While we also found that there was this alleles of secession between the single GGHFR, as I said it earlier, was significantly associated with in children less than five who could define in the single mutant that was directly associated with treatment failure. That was not recommended in GSFR with codon 108. We also recommended that there was no significant

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relationship between the triple mutant or the double GSFR in-patient that were over five years old. So, most many of the patients who were above five years old and that had some [misspelled?] of [misspelled?] was originally had some levels of resistance to falciparum parasite. Next slide.

So in conclusion one we had that the difference of mutation in GHFR a GHPS. And the prevalence rate of antibodies that is now [misspelled?] I think. Of SP Nigeria is of [misspelled?] and Mozambique by generally it is here. The National [misspelled?] government adopted ACT as a new policy in Nigeria and we'd also from this study conclude that the codon mutant GHFR and GHPS could be used as a subset predictive marker of treatment failure in Nigeria. While we can also recommend that the age of [misspelled?] is an immediate factor in falciparum parasite during the treatment of SP in moderate and high malaria area. Next slide.

While completely you can say the quintuple mutant was about 29 percent by the [misspelled?] and the failure rate was about 25 percent using the adjusted genotype index as depicted and proposed by Giente Atal [misspelled?] 2002. We had a high index of 1.07, this was low compared to other study that was coming out in Mozambique that had about 2.07, and in Uganda there was 1.9. So we computed that as using the [misspelled?] used the age-adjusted [misspelled?] as a

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model of monitoring the SP resistance would be a valuable tool to monitor the resistance across Africa. So we still believe that further work is needed for the data of age-adjusted jury in order and to make certain in Africa. Next.

Well I want to thank my boss for showing the [misspelled?] of apologies in collating of the medicine. Dr. Grace Gbotosho is my supervisor, Dr. [misspelled?] is my treater [misspelled?] and Omar [misspelled?] and my professor [misspelled?], Professor Dyann, I say thank you very much and thank you for the invitation.

[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Thank you very much. Dr. Tom Mayor just gives us this situation for consideration in Nigeria just to remind you that before that we had the desacrution [misspelled?] for chloroquine in the Cameroon and ITTI in Southern African and also consider in Mozambique. Dr. Tom Mayor has some time for some questions. Yes, sir.

**MALE SPEAKER:** Hi. Based on what you have showing here, would it be consider like the receptor for DHFR, what will all the other five mutations on the DHFR and DHPS as valuable marker as SP further in Nigeria for children and the five years of age?

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**DR. ERNEST TAMBO:** Yeah. In the little we are efficiently used if when the patient outcome used as a predictive of treatment failure. And if that is recommended, we know the risk group are the children under the age of five, which the [misspelled?] have clearly showed to us that in [misspelled?] are more than five years or to 12 years of age that are that can have twenty years of a marker as a predictive, can be used as a predictor of treatment failure. They can be allowed to. But I think our effort is trying to validate all that [misspelled?] and not only that method, also tried to use the age at the model to see how significantly we can see how we can investigate that in all. How?

**MALE SPEAKER:** I just want to make some qualifications; I think you didn't answer the last question very well. I think the absolute data [misspelled?] who used all this signification that you showed on the slide as markers as precedence in children, that's in five years. I think it is clear from the data, I don't know if you have called all the children with single [misspelled?] mutation actually for treatment so you need to make that clearer. And on number [misspelled?] also that the whole idea of looking at molecular markers is actually a tool that can be used for epidemiological service for therefore, that's a reason why we

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are doing the education satisfaction analysis to show if you have some mutation that can easily predict effectively, [misspelled?] and what age groups. That is what is the best because you are basing this information on [misspelled?] kept the children under the age of five, by the time you are going to use a codon factor, then the other [misspelled?] is lost. So I think you need to process this across the hospital.

**DR. ERNEST TAMBO:** Thank you.

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** Did no markers show? Thanks again.

[Applause]

**ROBERT GUIGUEMDE (BOBO-DIOULASSO):** This is the last paper for the session but before I close it, I would like to remind you that [misspelled?] message for today will be on genomes and for tomorrow it will actually be on mosquitoes. On behalf of my co-chair and myself, thanks for your attendance. Good afternoon.

[Applause]

[END RECORDING]