



The American Society of Tropical  
Medicine and Hygiene  
**56th Annual Meeting**

## SYMPOSIUM HIGHLIGHTS

# Patients Benefit from Artemether/Lumefantrine Community Deployment



### **Symposium Session:**

Tuesday, November 6th, 2007  
8:00 am - 9:45 am, Salon AB

### **4th-8th November 2007**

Philadelphia Marriott Downtown  
Philadelphia, Pennsylvania USA

# Patients Benefit from Artemether/Lumefantrine Community Deployment



**Artemether/Lumefantrine was the first fixed-dose artemisinin combination therapy (ACT) to be approved by stringent regulatory authorities as early as 1999, and is the only WHO pre-qualified ACT. Since 2001, over 130 million treatment courses have been supplied to the public sector of malaria endemic developing countries, and 28 countries have adopted Artemether/Lumefantrine as first-line treatment. There is growing evidence that including this ACT in malaria control programs is a cost-effective way of significantly reducing morbidity and mortality<sup>1-4</sup>.**

**3** Chair  
Ambrose Talisuna

This symposium reported encouraging successes from several African nations, providing proof that rolling back malaria and saving lives is an achievable goal.

**5** Changes in Inpatient Pediatric Malaria Case Load at Macha Hospital After the Introduction of Artemether/Lumefantrine in a Rural Zambian Community  
Philip Thuma

**9** Nigeria: Final Analysis on the Trend in Hospital Admissions of Children with the Introduction of Artemether/Lumefantrine  
Ambrose Talisuna on behalf of Henry Akpan

**11** Long-term Follow up of South African Malaria Control Interventions  
Charlotte Muheki  
Zikusooka

**15** The Evaluation of Artemether/Lumefantrine Implementation in Tanzania (ALIVE project): Key Issues and First Results  
Blaise Genton

1. Barnes K, Durrheim D, Little F et al. Effect of Artemether-Lumefantrine Policy and Improved Vector Control on Malaria Burden in KwaZulu-Natal, South Africa. *PLoS Med.* 2005; 2(11): e330
2. Chanda P, Masiye F, Bona M, Chitah B et al. A cost-effectiveness analysis of artemether lumefantrine for treatment of uncomplicated malaria in Zambia. *Malaria Journal* 2007; 6:21:
3. Akpan H. Analysis on the trend in out-patient visits and hospital admissions of children with the introduction of Artemether/Lumefantrine in Nigeria. Poster presented at ASTMH 2007, Philadelphia, USA.
4. Lemma H. Community Deployment of Artemether/Lumefantrine with Rapid Diagnostic Tests (RDTs) in Tigray, Ethiopia. Poster presented at ASTMH 2007, Philadelphia, USA.

**Chair: Ambrose Talisuna**

Ministry of Health in Uganda



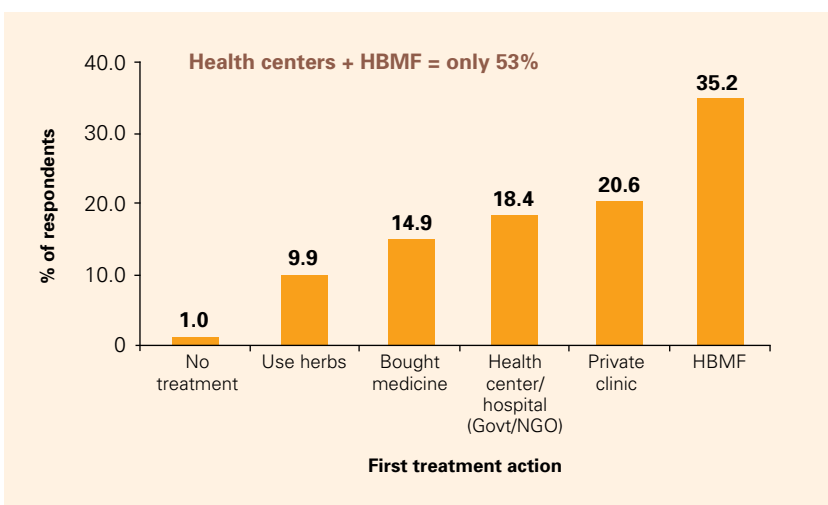
**Ambrose Talisuna** opened the symposium by describing the history of ACTs being adopted as first-line therapy for uncomplicated falciparum malaria.

By the year 2000, ACTs were recognized as an effective therapy for falciparum malaria. As late as 2003, only four countries in Africa had an optimal antimalarial drug policy. The turning point came in January 2004, when an article was published in *The Lancet*, written by prominent thought leaders in the arena: a constructive criticism of the lack of policy change. One year later, 34 countries had adopted ACT therapy thanks to strengthened technical recommendations and financial support from the Global Fund in Round 4. Today, almost the entire African region has adopted ACTs as first or second line therapy.

However, new drugs and new policies are only part of the solution. Effective delivery of these treatments to those that need them most is crucial to achieve a significant impact on malaria morbidity and mortality. Two areas which need improvement are illustrated by recent data from Uganda and Zambia.

In Uganda, only about 50% of the target population is accessing malaria treatment, through a combination of health care centers and home-based management.

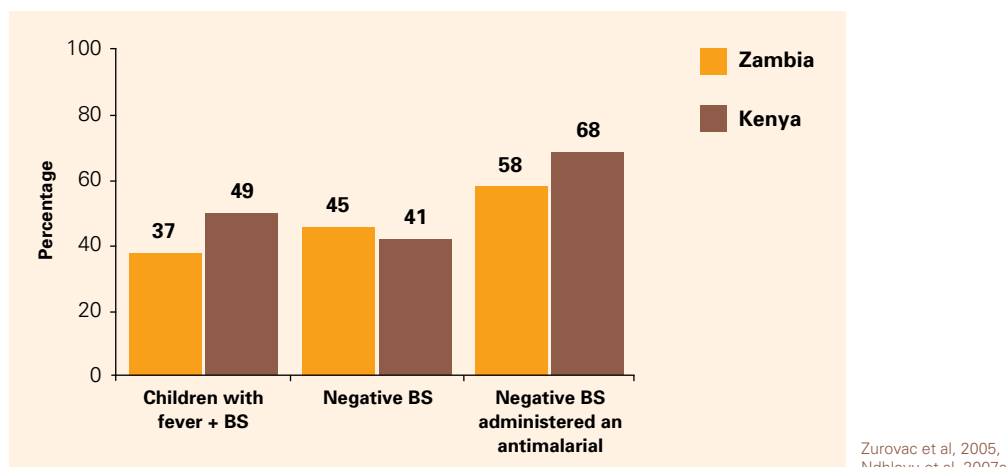
**Treatment actions for febrile children...where are we in Rakai Uganda?**



Mugaga et al, 2007

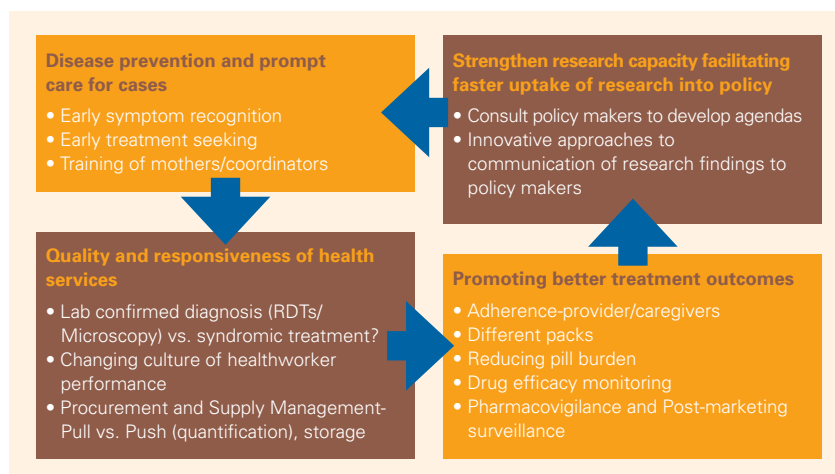
In Zambia and Kenya, around 60% of patients with fever, but a negative blood slide, are given antimalarials – medication that they do not need and which will not be effective for them.

### Adherence to laboratory results by HWs



Dr Talisuna described what he regards as the critical pillars for scaling up access to effective antimalarial treatment for impact.

### Critical pillars



These pillars need to be looked at within a pro-poor framework that considers equity, gender, capacity building, knowledge dissemination, and policy development.

“ There is evidence that ACTs are having impact. Maybe there is some light at the end of the tunnel! ”

Zanzibar, Kwazulu Natal, Zambia, the Tigray region in Ethiopia; more recently Rwanda, Tanzania, Kenya and Mozambique all have evidence for the impact of ACTs on malaria, and other countries are currently analyzing their data. Some key data were presented during this symposium.

**Philip Thuma**

Malaria Institute at Macha

## Changes in Inpatient Pediatric Malaria Case Load at Macha Hospital After the Introduction of Artemether/Lumefantrine in a Rural Zambian Community



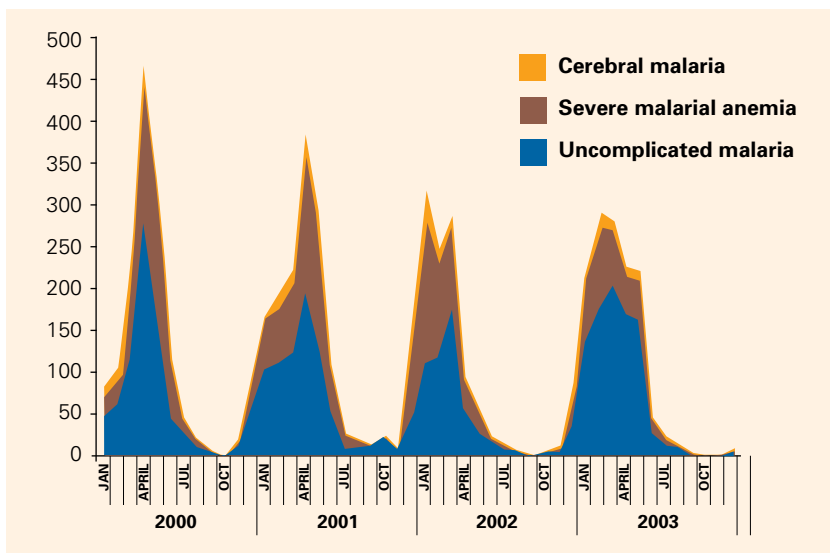
**Philip Thuma** reported findings from the Malaria Institute at Macha, which is based at a rural hospital in Choma District, Southern Province of Zambia, serving a population of approximately 160,000 people. The institute has been conducting malaria research and collecting data prospectively for over 15 years.



In 2004, dramatic changes in the pattern of children’s ward admissions (under age 6 yrs) for malaria cases and malaria-related deaths were seen at Macha Hospital.

Malaria is seasonal in Macha. Rains in November and December are followed by outbreaks of malaria which tend to peak in March and April.

### Macha hospital – Under 5 hospitalized malaria cases



The majority of malaria cases are uncomplicated, although the graph shows that there is a fair proportion of severe anemia (Hb ≤5g/dL).

In June 2003, there was a press release by the Zambian government introducing the new policy of phased introduction of Artemether/Lumefantrine. In fact, this ACT had already been distributed and used in 7 out of the 72 districts of the country earlier that year, in February. One of those districts receiving Artemether/Lumefantrine earlier was Kalomo, which borders Choma, and feeds patients into Macha hospital. Therefore, Macha hospital was exposed to patients who had received Artemether/Lumefantrine before some of the other hospitals in the country.

In the 1980s and 1990s, there were around 500 malaria discharges from Macha hospital per year. In the late 1990s and early 2000s, there was a surge in malaria cases due to increasing chloroquine resistance, to around 1400 cases per year. Then in 2004, the numbers of cases dropped sharply.

### Children’s ward malaria discharges at Macha hospital

Year	Malaria discharges
1984	559*
1994	575
2000	1,479
2001	1,778
2002	1,294
2003	1,418
2004	<b>423</b>
2005	<b>123</b>

\* Ages 0 – 14 years

### Children’s ward malaria deaths at Macha hospital

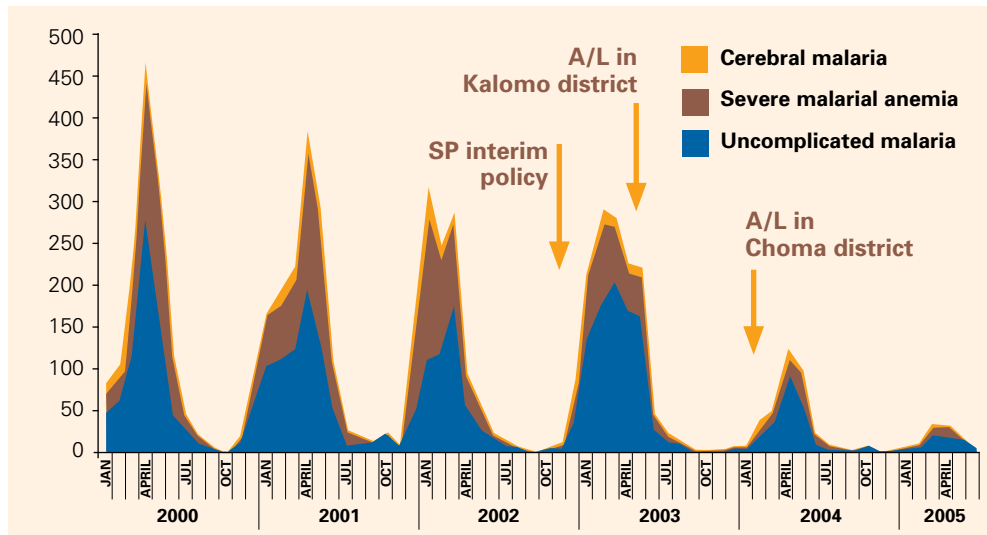
Year	Malaria deaths
2000	106
2001	65
2002	32
2003	34
2004	<b>18</b>
2005	<b>6</b>

The death rate had been dropping throughout 2002/2003, but in 2004 and 2005 a dramatic reduction was seen.

“ A few years before, we had seen 3 or 4 children die every day, and many children on blood transfusions. In comparison, in 2004, we felt as if we were unemployed. ”

Phil Thuma explained that the hospital had started to use SP in late 2002 as an interim policy, recognizing that chloroquine was no longer effective. This did have a positive effect, reducing the proportion of severe malaria to uncomplicated malaria in 2003. Then Artemether/Lumefantrine was introduced first in Kalomo in 2003 and then in Choma by early 2004. These changes in drug treatment preceded the dramatic drop in case load.

### Drug treatment interventions and corresponding malaria cases



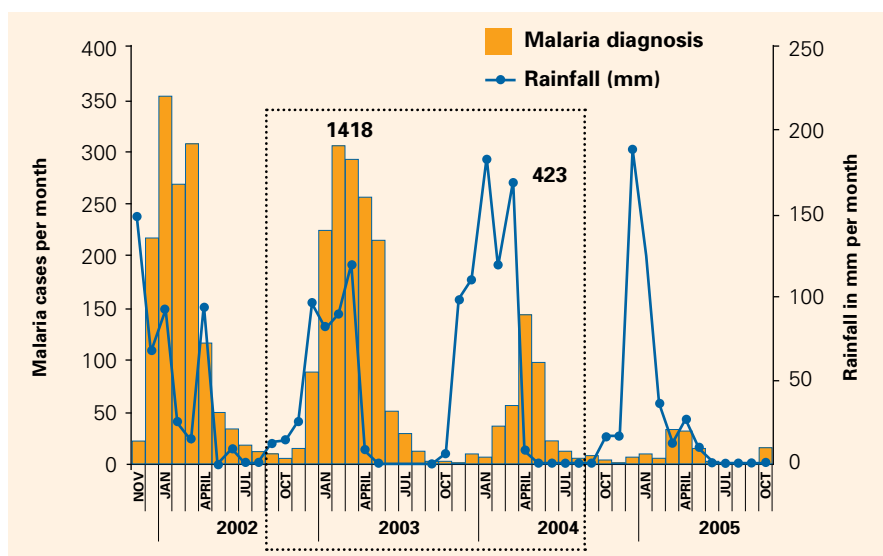
“ I can't show that the introduction of Artemether/Lumefantrine and the corresponding reduction in malaria case load are cause and effect – but there seems to be a strong relationship. ”

Could factors such as bed net distribution, IRS (Indoor Residual Spraying), IPT (Intermittent Preventative Treatment) in pregnancy have influenced this data? Climatic conditions may also have affected the case load – in periods of drought, the vectors of malaria do not breed very well.

- Over this same time period, the overall amount of non-malaria diagnoses has remained the same, indicating that the population using the hospital at Macha has probably not changed.
- IRS has not yet been implemented in this rural district.
- IPT has been used in pregnancy since 2001, but this wouldn't really make a difference to malaria cases in children.
- Around 15% of households were using ITNs (Insecticide Treated Nets) in 2004 – but this is much too low to explain the dramatic change in malaria case load. Data show that coverage has to be around 80% before changes are seen in community levels of malaria. In Choma, ITNs have only just been distributed in 2007.
- In 2004, when the dramatic drop in malaria case load was seen, rainfall was higher than the previous year. There was a drought in 2005, which may have influenced the drop in malaria cases seen between 2004 and 2005.

In early 2006, stock-outs of Artemether/Lumefantrine were experienced at many rural hospitals and health centers, including Macha. The malaria case load immediately shot up, and malaria deaths quadrupled.

### Macha hospital – Pediatric malaria cases vs. rainfall



### Macha hospital – cases of malaria increased!

Year	Discharges
2001	1,778
2002	1,294
2003	1,418
2004	423
2005	123
<b>2006</b>	<b>565</b>

In summary, the malaria case load and deaths dropped dramatically (nearly 10-fold) in 2004 following the introduction of Artemether/Lumefantrine. Conversely, stock-outs, and reversion to SP use, resulted in a four-fold increase in cases and deaths in 2006.

The possibility therefore exists that the introduction and widespread use (and then subsequent “outage”) of Artemether/Lumefantrine, contributed to the changes in pediatric malaria case load seen at Macha Hospital.

## Henry Akpan

National Malaria Control Program, Federal Ministry of Health, Abuja, Nigeria

# Nigeria: Final Analysis on the Trend in Hospital Admissions of Children with the Introduction of Artemether/Lumefantrine

This data was presented by the Chair, **Ambrose Talisuna**, on behalf of **Henry Akpan**, of the National Malaria Control Program, Federal Ministry of Health, Abuja, Nigeria, who was unable to attend.

Malaria is endemic in Nigeria, with 50% of the population having at least one attack per year, and around 66% of all clinic attendance and 30-50% of hospital admissions being attributed to malaria.

Artemether/Lumefantrine was distributed free of cost in April 2006 initially to 18 states, then to the remaining 19 states in August of the same year.

Public health facility assessment in October 2006 in Delta state (supported by Global Fund) and Akwa Ibom state (not supported by Global Fund) showed significant improvement in the use of outpatient services following the introduction of Artemether/Lumefantrine.

Data on hospital admissions to pediatric wards for the two states before and after Artemether/Lumefantrine introduction for treatment of malaria were analyzed. All malaria cases admitted to hospital were parasite-confirmed.

Children diagnosed with malaria often had other diseases, so had a 'malaria plus' diagnosis. Common diagnoses were as follows:

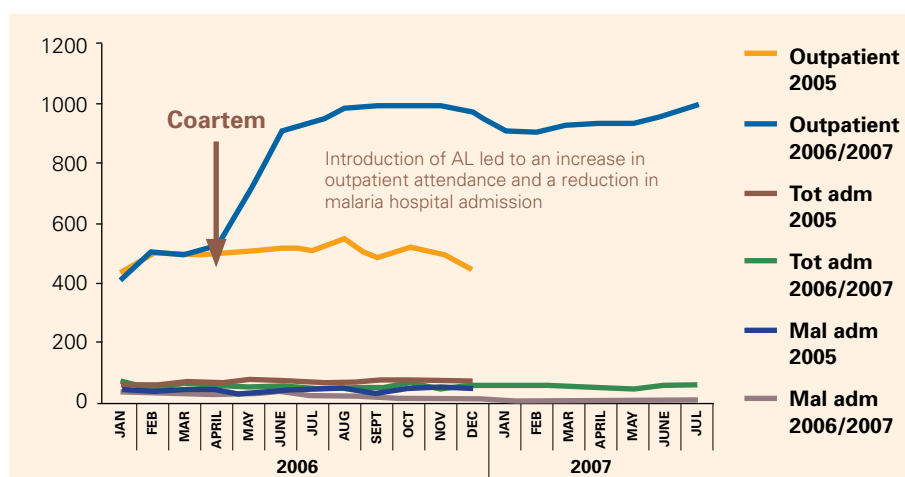
- Malaria alone
- Malaria + anemia
- Malaria + gastroenteritis (most common)
- Malaria + septicaemia
- Febrile convulsion secondary to malaria
- Malaria + acute respiratory tract infection (ARI)

Most of the children admitted were below 5 years of age, confirming this group to be the most vulnerable for severe malaria.

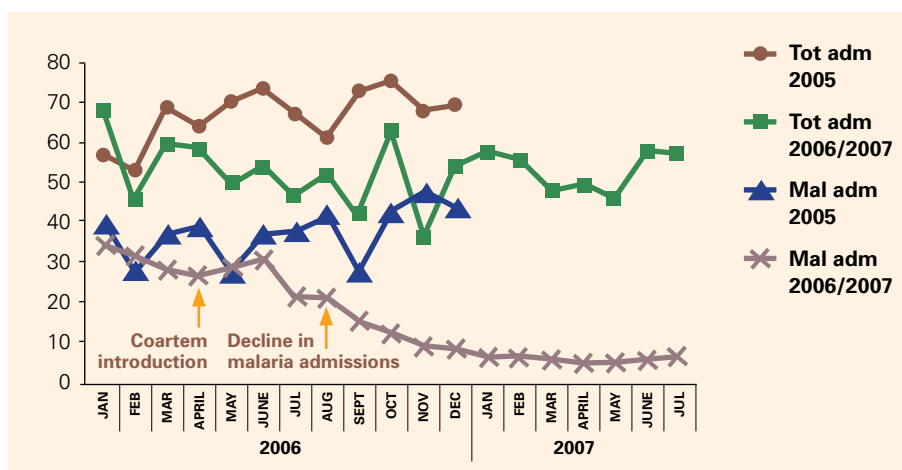
The results revealed that the use of public health facilities greatly improved in the states where Artemether/Lumefantrine had been distributed. From the introduction of Artemether/Lumefantrine in April 2006, outpatient attendance almost doubled, while pediatric malaria hospital admissions reduced proportionately.

Malaria admissions declined notably within 4 months of the introduction of Artemether/Lumefantrine in April 2006, and this trend continued into 2007.

## Trend in outpatient attendance and malaria hospital admission



### Malaria admissions reduced with AL use



### Summary of trend in hospital admissions with AL introduction

	Total Hospital Admissions	
	2006	2007
Children under 5 yrs	83%	89%
Children > 5yrs < 14yrs	17%	11%
% of child admissions due to malaria	43%	13%
% admissions in children < 5 due to malaria	79%	65%
% admissions in children > 5 due to malaria	21%	35%

**In conclusion, the introduction of free Artemether/Lumefantrine encouraged increased use of out-patient health facilities to obtain the drug for children with malaria, and as a consequence significantly reduced hospital admissions of young children with severe malaria. This is expected to lead to a reduction in malaria under-5 mortality, and therefore a reduction in all-cause under-5 mortality.**

#### Question: How was the availability of Artemether/Lumefantrine publicized?

**Obiyo Nwaiwu** (Pediatrician, Novartis Nigeria): Before the introduction of Artemether/Lumefantrine, healthworker training was held, both at a central and a local government level. Information about free Artemether/Lumefantrine and the policy change from chloroquin/SP was spread through town criers and local radio. Previously, use of public health facilities incurred a user fee, and any drugs dispensed had to be paid for. Advertising free antimalarials attracted an increased attendance at these out-patient facilities, from patients who previously would have consulted informal health care providers, such as herbalists.

## Charlotte Muheki Zikusooka

HealthNet Consult, Kampala, Uganda

# Long-term Follow up of South African Malaria Control Interventions

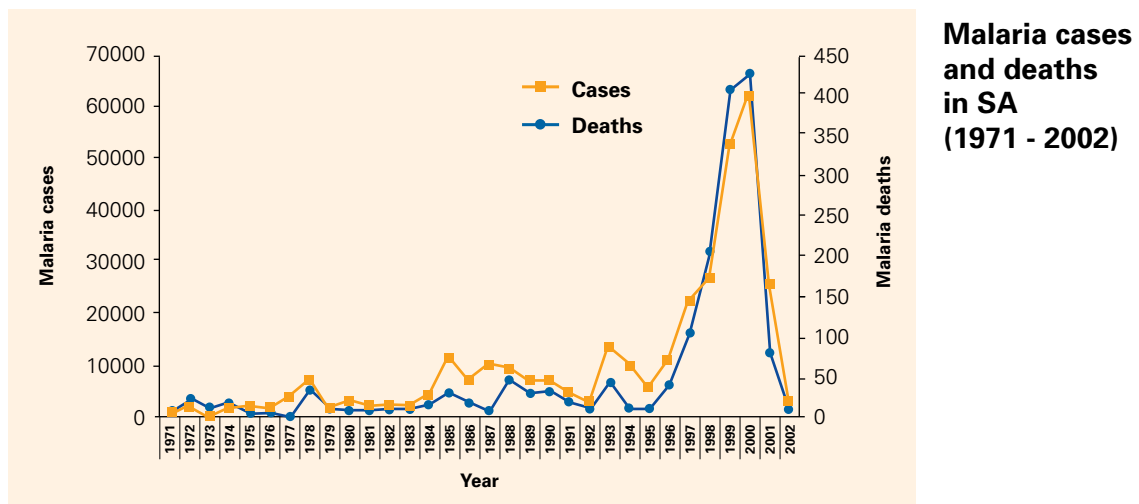


**Charlotte Muheki Zikusooka**, of HealthNet Consult, Kampala, Uganda reported on the long-term benefits of using ACTs in South Africa.

“ Kwazulu Natal is probably one of the most renowned success stories of malaria control in Africa. ”

Out of the nine provinces in South Africa, only three are affected by malaria: Kwazulu Natal, Limpopo and Mpumalanga. Kwazulu Natal (KZN) historically had the highest prevalence of malaria out of the three. By the year 2000, 65% of all malaria cases in South Africa were found in KZN.

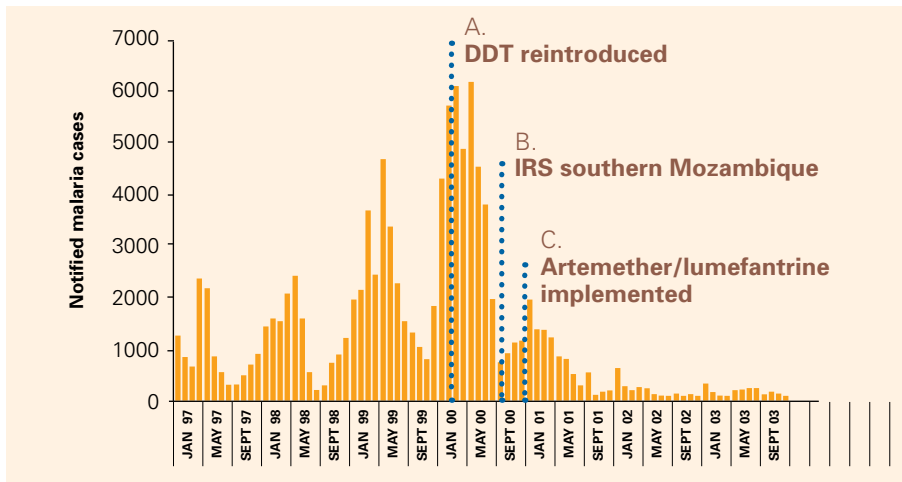
The graph below gives an overview of malaria cases and deaths in South Africa between 1971 and 2002. Over the course of 20 years, malaria grew from a minor to a major problem, peaking in the year 2000, after which the number of cases dropped sharply.



In KZN, three important malaria control interventions were implemented in rapid succession in 2000 and early 2001:

- **Improved vector control** DDT was re-introduced in April 2000, to eliminate vectors which had become resistant to one of the pyrethroids in use. DDT spraying can only be used in traditionally built structures, accounting for about 40% of the houses in KZN.
- **Vector control in southern Mozambique** IRS (Indoor Residual Spraying) was introduced later in the same year, 2000. Many malaria cases had resulted from migration across the border from Mozambique to KZN.
- **Change of first-line treatment for malaria to Artemether/Lumefantrine** By the year 2000, data was showing that SP was failing in 88% of malaria cases. This prompted the change in treatment policy from SP to Artemether/Lumefantrine at the beginning of 2001.

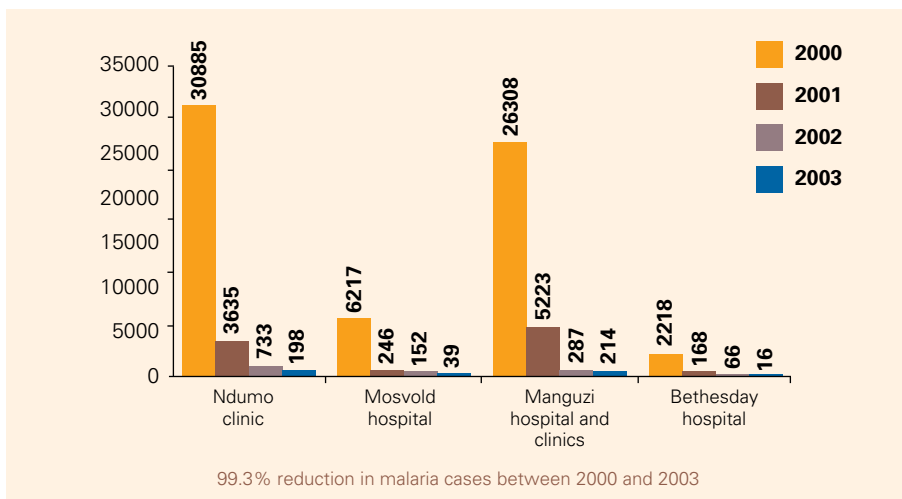
### Number of malaria cases in KZN in relation to timing of significant malaria control interventions



This graph illustrates the seasonality of malaria and the increase in the number of cases over the years until the sudden drop after the year 2000.

There was a dramatic drop in malaria cases across four hospitals in KZN within 1 year of implementing the three interventions, with a 99.3% reduction in malaria cases between 2000 and 2003.

### Malaria cases in selected health facilities – KZN

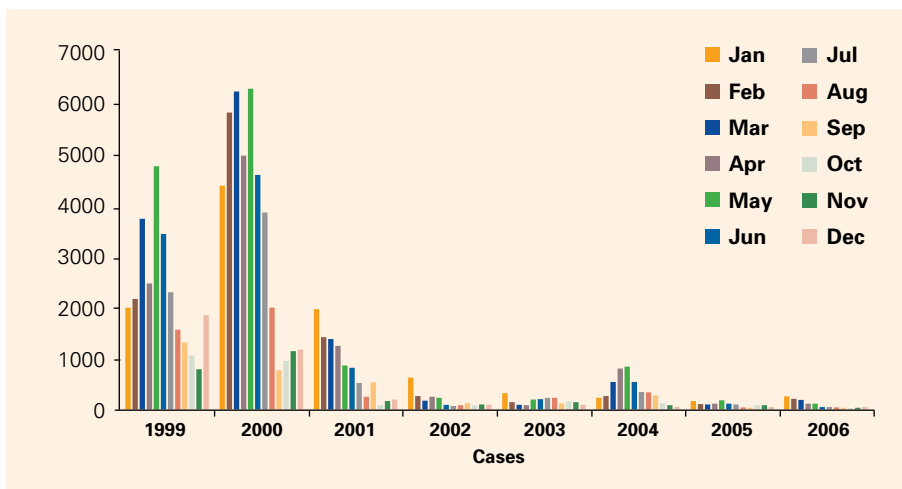


In addition, there was a 98.6% reduction in malaria admissions, and 97.3% reduction in malaria deaths between 2000 and 2003.

“As researchers, we asked ourselves – to what can we attribute this dramatic benefit? Which intervention?”

The reductions in malaria cases have been maintained since 2003. In 2004, an unexpected resurgence was seen, which can be explained by emergence of vector resistance to the remaining pyrethroid being used for spraying alongside DDT, and also by the use of faulty rapid diagnostic tests, leading to false malaria cases being reported. The pyrethroid was replaced by a carbamate.

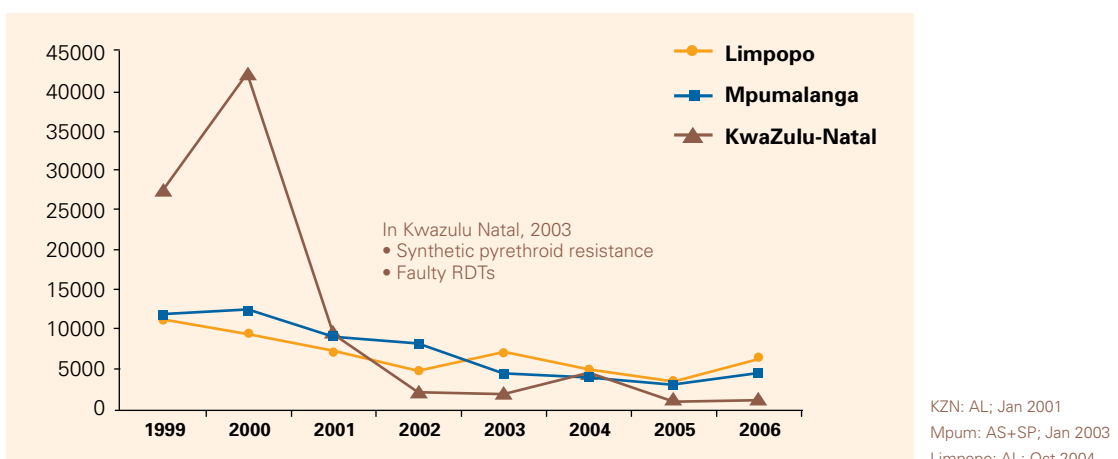
**Trends in malaria cases in KZN 1999 - 2006**



Malaria deaths since 2003 have also remained at the low level seen in previous years.

To try and elucidate how much of the reduction in malaria can be attributed to each different intervention, we compared malaria cases across the three provinces in South Africa.

**Trends in malaria cases in 3 provinces in SA**



KZN was the first of the provinces to use ACTs, in 2001. Mpumalanga followed in 2003, and Limpopo in 2004. KZN used to have the highest malaria incidence of the three provinces, but since 2004 has had the lowest.

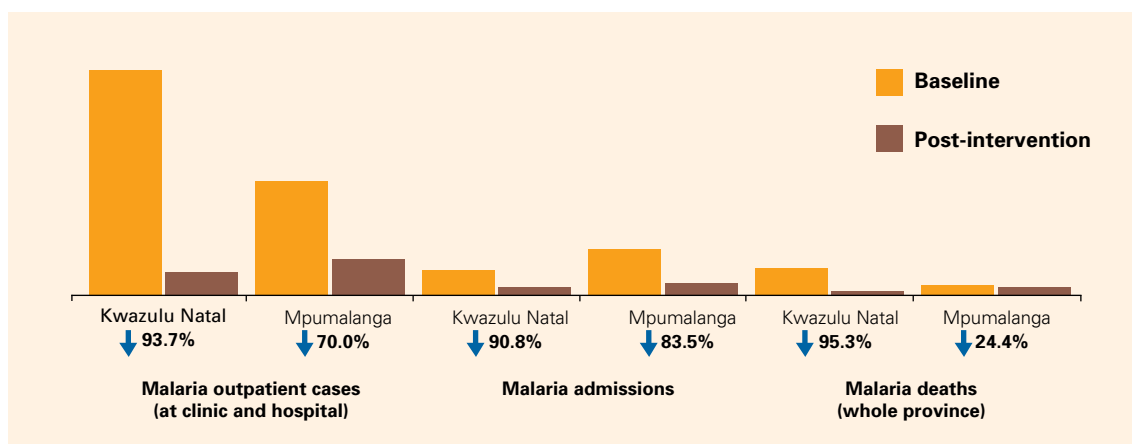
A Delphi survey was conducted, consulting experts worldwide in the three interventions and also in case management, to try and understand to what extent each intervention played a role in reducing the malaria burden in KZN.

Average responses revealed that the treatment policy change to Artemether/Lumefantrine was responsible for:

- 36% reduction in malaria cases
- 46% reduction in malaria admissions
- 62% reduction in deaths

The opportunity was taken to compare the results of Mpumalanga, where existing malaria control interventions continued alongside the treatment policy change to AS/SP but no new interventions were introduced; and KZN, where the three malaria control interventions were implemented within a short time.

### Comparing impact of AL in Kwazulu Natal and AS + SP in Mpumalanga on health outcomes



The graph shows that in KZN, malaria admissions were reduced by 90%, with the three malaria control interventions, and in Mpumalanga, where only the treatment policy was changed, malaria admissions were reduced by 83%. If the only difference between the two provinces is in the number of interventions, this gives reason to believe that the change in treatment policy had a relatively much higher contribution to malaria admissions and cases than concluded by the Delphi survey.

The difference seen in reduction of malaria deaths is partly due to different reporting systems, and is not covered fully in this presentation.

Although climate was initially thought to contribute, other studies (Craig et al 2004) did not find a significant relationship between climatic factors and malaria incidence in Kwazulu Natal.

**In conclusion, Kwazulu Natal is a very successful story of malaria control, reducing malaria cases and deaths through the implementation of several interventions. The Delphi survey estimates were conservative, and a greater proportion of the improvement in malaria outcomes should be attributed to the change of drug policy to Artemether/Lumefantrine.**

## Blaise Genton

Ifakara Health Research and Development Center, Dar es Salaam, United Republic of Tanzania

# The Evaluation of Artemether/Lumefantrine Implementation in Tanzania (ALIVE project): Key Issues and First Results



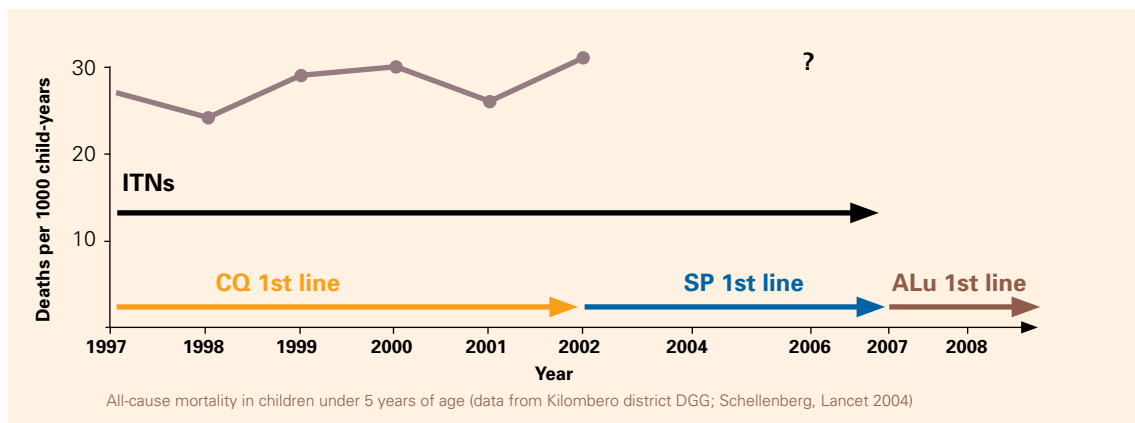
**Blaise Genton**, of Ifakara Health Research and Development Center, Dar es Salaam, United Republic of Tanzania presented the ALIVE study design and objectives.

“ Why do we use ACTs for malaria treatment? Because they have excellent efficacy against multi-resistant plasmodium parasites; we can thus expect less severe malaria, and less reattendances. ”

The ambitious acronym ALIVE stands for **A**rtemether/**L**umefantrine **I**n **V**ulnerable populations: **E**xploring health impact. This is a community-based study, to assess the impact of Artemether/Lumefantrine when used as first-line therapy on malaria mortality and morbidity. It is a joint project between the Ifakara Center, the Swiss Tropical Institute, Novartis Pharma AG and the Novartis Foundation for Sustainable Development.

Ifakara is in a highly malaria endemic area. The hypothesis is that the efficacy of ACTs should result in fewer cases of severe malaria, fewer hospital admissions, fewer treatment failures and a reduction in overall and malaria-specific mortality as well as overall and specific health facility attendance, as compared with the SP era.

### All-cause mortality in children under 5 years of age



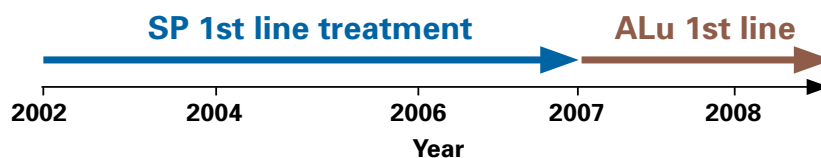
The other hypothesis is that ACTs should reduce malaria transmission, through reduction of gametocyte carriage, as was shown in Kwazulu Natal in 2001.

## Study design

The design of the study is a longitudinal, prospective, community-based surveillance of demographic (population of 82,000) and health center (15 public health facilities) data.

The sample size of 82,000 people gives the power to detect a difference of 15% in decrease of under-five mortality. If Artemether/Lumefantrine achieves this reduction, it will be an outstanding result. This surveillance started in 2002, and will continue until 2009.

The primary objective of the ALIVE study is to assess the impact of Artemether/Lumefantrine as first-line policy on all-cause mortality in children under 5 years in rural Tanzania, in comparison with historical data during the SP era.



The secondary objective is to look at malaria-related mortality in children under 5, all-cause and specific morbidity, health center attendances, anemia incidence in the community and patient satisfaction with and adherence to Artemether/Lumefantrine.

This study is being conducted in co-operation with the ACCESS project of the Novartis Foundation, which is assessing health-seeking behavior and actual patient access to treatment following a health facility visit.



To explore the impact of Artemether/Lumefantrine on malaria transmission, two cross-sectional surveys will be conducted in 2008 and 2009 to compare parasite and anaemia prevalence rates in the general population with the surveys conducted in 2005 and 2006 in 1,000 people.

Assessing Artemether/Lumefantrine adherence, acceptability and feasibility will be through questioning 500 malaria patients, selected 100 at a time following 1st, 2nd, 3rd dose etc.



Embedded in the study is a pharmacovigilance system. All health workers have been trained to be aware of potential drug-related adverse events and to use the TFDA (Tanzania Food and Drug Authority) forms and the Novartis reporting system for serious adverse events.

## Potential confounding factors

South Africa and Zambia are the only two countries with sufficient history of ACT use to assess the impact of treatment policy on malaria. The confounding malaria control interventions seen in these two studies, IRS (Indoor Residual Spraying) and ITN (Insecticide Treated Net) use will not be present in this study.

In the area of demographic surveillance, ITN use has been in place since the late 1990s, and coverage has been increasing towards 80% (the level considered sufficient to have an impact). So the effect of ITN use should already have been shown prior to the introduction of Artemether/Lumefantrine. Large-scale re-treatment of all nets in the area may happen in 2008, which may be a confounding factor. IRS has not and will not be implemented in the area.

Another confounder may be the HIV prevalence (10%). Antiretroviral therapy was introduced for adults in 2005. It is only now starting to be introduced for children, which may constitute another confounding factor for under 5 mortality.

Currently there is no reliable malaria diagnosis in the health facilities. RDTs (rapid diagnostic tests) are being introduced in only four of the 15 facilities involved in the study, which will be a confounding factor. A dramatic reduction in malaria diagnoses may be seen in these centers, which could be due to Artemether/Lumefantrine or to the new ability to accurately diagnose true malaria.

**In conclusion, data collection for this important study will be on-going until Q2 2009. We hope the study will reveal vital information on the impact that Artemether/Lumefantrine is having on malaria cases, mortality and transmission.**

### ALIVE study timelines

Main components of ALIVE	2007		2008				2009			
		Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
DSS mortality monitoring	Start Q1 2002 →									
Health facility statistics	Start Q1 2005 →									
Satisfaction/adherence										?
Hemoglobin/parasitemia										
Adverse drug reaction reporting	Start Q1 2002 →									

#### Question: What will be the comparator for anemia and malaria prevalence at the community level?

**Blaise Genton:** There are three surveys that have been conducted between 2004 and 2006 during the SP era. The data from these will be compared with the two surveys that we will conduct in 2008 and 2009. If there is a reduction in malaria transmission, we should see a reduction in parasite prevalence and hopefully an increase in hemoglobin levels, since malaria is the main contributor to anemia in this area.

## Summing up

**Charlotte Zikusooka:** Malaria in South Africa is always treated on the basis of confirmation – either RDT or microscopy. About 96% of all malaria patients seek care in public health facilities. ITNs are not widely used in South Africa, but are used in KZN. All the data that I presented was for all ages, not only under 5s. There is very little private sector healthcare available in KZN. There is no home-based management of fever strategy in KZN.

My key take-home messages:

- ACTs, in particular Artemether/Lumefantrine, have a key role in reducing the malaria burden in any area, and also has an impact on severe malaria, as hospital admissions decline, and on malaria deaths.
- We should use an integrated approach to malaria control – not just ACTs alone, but also IRS, ITNs and any other interventions proven to be useful.
- The data I presented from South Africa shows the extent to which a responsive, well-organized malaria control program can be successful – reacting quickly to changes in the malaria situation and responding appropriately.

**Phil Thuma:** In 2000/2001, I would have advocated very strongly for every child under 5 with a fever getting treated with antimalarials, because in those days community surveys showed a prevalence of 70-80% parasites. That has changed dramatically, and as these changes come about, we have to be quick to react so that we don't overuse these drugs.

I also echo the integrated approach. There is published data from Zimbabwe showing that effective vector control has changed the fitness of the parasite. There is also evidence that drug resistant genes within the mosquito change from when they are taken in the blood meal to when they emerge in the saliva. If that is true, then it makes sense to have good vector control, because we can decrease the pace at which parasites become resistant to drugs.

Early, effective therapy at the community level will markedly decrease the need for hospitalization and decrease child mortality due to malaria.

**Blaise Genton:** I believe in a holistic approach, and when you have a febrile child or adult, you have to look at all possible causes of fever. My take-home message is not access to treatment, but access to appropriate case management.

**Ambrose Talisuna:** When case load data goes up, we believe it, we send drugs, we spray. When the numbers go down, we question them and are a bit nervous. We need to improve our data to really assess the impact of malaria control interventions.

## Panel discussion

### Key points

- We have never had a drug like Artemether/Lumefantrine that works this quickly before, and which appears to have an effect on gametocyte carriage.
- There has been a huge emphasis on vector control, but we have forgotten about case management, and we now have a drug which is unique in the history of malaria control.
- The most important aspect in assessing impact of malaria control interventions is reliable malaria diagnosis; we should use a negative result to move forward with diagnosis and cover other possible diseases.
- We should use an integrated approach to malaria control –ACTs in addition to IRS, ITNs and any other interventions which have proved to be useful.



