

**EFFICACY AND SAFETY OF ARTEMETHER-LUMEFANTRINE
AND ARTESUNATE- AMODIAQUINE FOR TREATMENT OF
UNCOMPLICATED FALCIPARUM MALARIA IN MAINLAND
TANZANIA**

**PRELIMINARY FINDINGS
INVIVO 2011/2012**

D. Ishengoma & TETs Group

Background

- ALu was introduced Tanzania as first line treatment of uncomplicated falciparum malaria in November 2006 and become fully rolled out in January 2007
- Despite implementation of the new malaria guidelines, TETs were not been fully implemented as recommended by WHO
- Although the efficacy of ALu is still high, there is a threat of ACT drug resistance as recently confirmed in South-eastern Asia
- Thus, monitoring needs to be urgently intensified by NMCP and its partners

Artemisinin resistance

www.nature.com/nature/journal/v505/n7481/full/nature12876.html

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A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

Frédéric Ariey, Benoit Witkowski, Chanaki Amaratunga, Johann Beghain, Anne-Claire Langlois, Nimol Khim, Saorin Kim, Valentine Duru, Christiane Bouchier, Laurence Ma, Pharath Lim, Rithea Leang, Socheat Duong, Sokunthea Sreng, Seila Suon, Char Meng Chuor, Denis Mey Bout, Sandie Ménard, William O. Rogers, Blaise Genton, Thierry Fandeur, Olivo Miotto, Pascal Ringwald, Jacques Le Bras, Antoine Berry * et al.

Affiliations | Contributions | Corresponding authors

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The spread of resistance to artemisinin in isolates of the malaria pathogen *Plasmodium falciparum* in southeast Asia threatens to undermine efforts to eliminate the disease around the world. The import...

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NATURE | NEWS

Resistance gene identified in malaria parasite

Discovery of mutations that neutralize artemisinin leads to efforts to chart their spread in southeast Asia.

Ewen Callaway
18 December 2013

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Mutations in the malaria parasite that underlie its resistance to the potent drug artemisinin have been pinpointed for the first time. By testing for these genetic variants, public-health officials now plan to map malaria strains that are impervious to the drug in southeast Asia, with the hope of stemming their spread to Bangladesh, India and Africa.

"If full-blown artemisinin resistance were to reach Africa, it could be, truly, a global health disaster."

MARCH OF RESISTANCE

Percentage of positive cases on day 3
0-3
3-9.9
10-19.9

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Malaria: Resistance nailed

Christopher V. Plowe
Nature 505, 30–31 (02 January 2014) | doi:10.1038/nature12845
Published online 18 December 2013

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A series of *in vitro*, genomic, ecological and epidemiological studies has pinpointed gene mutations in the malaria parasite *Plasmodium falciparum* that play a key part in resistance to artemisinin-based antimalarial drugs. **See Article p 50**

Subject terms: Parasitology · Diseases · Epidemiology · Genetics

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Artemisinin resistance

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"If full-blown artemisinin resistance were to reach Africa, it could be, truly, a global health disaster," says a WHO spokesman.

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Percentage of positive cases on day 3

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Objective



To assess the efficacy and safety of artemether/Lumefantrine (ALu) and Amodiaquie/artesunate (ASAQ) at 8 sentinel sites under NMCP

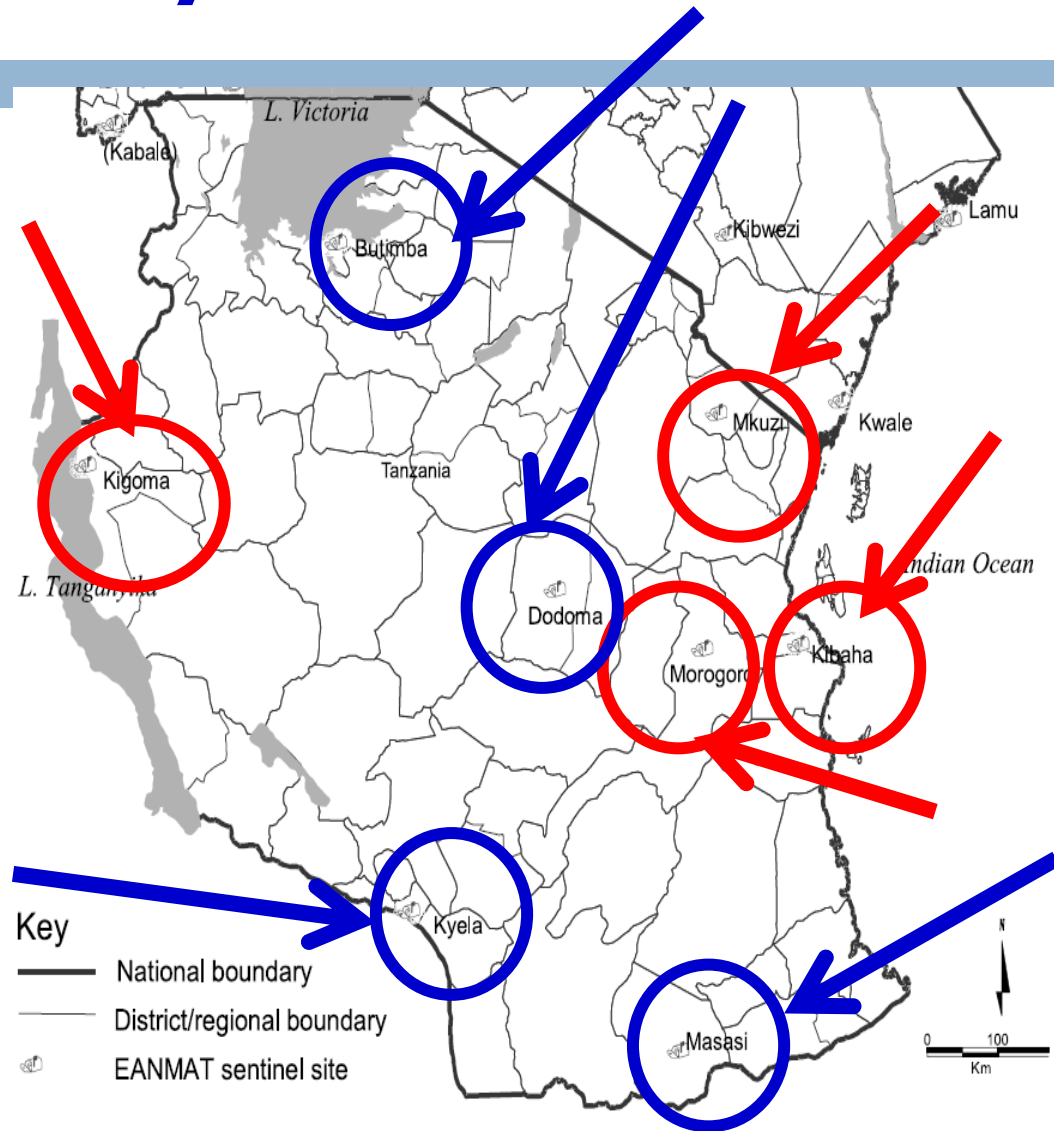
Methods... 1

- Design: open label, single arm in-vivo efficacy studies
- Studies were based on WHO protocol of 2009
- Target:
 - 88 children per site
 - Age
 - In 2011: 6 – 59 months with *P. falciparum* mono-infection + other WHO criteria.
 - 2012: 6 months to 10 years



Methods...2: Study sites

- 8 NMCP Sentinel sites
- 2011 (RED)
 - ▣ Mkuzi, Mlimba, Kibaha and Ujiji
- 2012 (BLUE)
 - ▣ Butimba, Nagaga (Masasi), Kyela and Chamwino



Methods...3

Study drugs

■ 2011

- ALu - Mkuzi and Mlimba
- AQAS - Ujiji and Kibaha

■ 2012

- ALu was used at all sites.

□ Follow-up: 28 days

□ Primary end point :

- Day 28 cure rates, uncorrected and PCR corrected for recrudescent Vs new infection

Results 1: Invivo 2011...ASAQ

□ In 2011-Ujiji-Kigoma

SUMMARY OF CLASSIFICATION PCR-CORRECTED				
	N	Proportional	Lower 95% CI	Upper 95%CI
ETF	0	0.000	0.000	0.073
LCF	0	0.000	0.000	0.073
LPF	0	0.000	0.000	0.073
ACPR	49	1.000	0.927	1.000
Total	49			
WHT	15			
LCF	7	0.310		
Total	71			

□ In 2011-Kibaha

SUMMARY OF CLASSIFICATION PCR-CORRECTED				
	N	Proportional	Lower 95% CI	Upper 95%CI
ETF	0	0.000	0.000	0.132
LCF	0	0.000	0.000	0.132
LPF	0	0.000	0.000	0.132
ACPR	26	1.000	0.868	1.000
Total	26			
WHT	1			
LCF	3	0.133		
Total	31			

Invivo 2011... ALU

2011 - Mlimba -Kilombero

SUMMARY OF CLASSIFICATION PCR-CORRECTED				
	Number	Proportional	Lower 95% CI	Upper 95%CI
ETF	0	0.000	0.000	0.522
LCF	0	0.000	0.000	0.522
LPF	0	0.000	0.000	0.522
ACPR	5	1.000	0.478	1.000
Total	5			
WHT	0			
LCF	0	0.000		
Total	5			

2011 – Mkuzi Tanga

SUMMARY OF CLASSIFICATION PCR-CORRECTED				
	N	Proportional	Lower 95% CI	Upper 95%CI
ETF	0	0.000	0.000	0.119
LCF	0	0.000	0.000	0.119
LPF	0	0.000	0.000	0.119
ACPR	29	1.000	0.881	1.000
Total	29			
WHT	0			
LCF	2	0.065		
Total	31			

2011 - Summary findings...

- Efficacy at all sites was $>95\%$
- No early treatment failure
- Late parasitological failure
 - Seven patients.
- Late clinical failure
 - Nine patients.
- PCR adjustments
 - 13 new infections
 - 2 negative PCR
 - 1 sample missing

Invivo 2012... ALu (all sites)

□ In 2012- Chamwino-Dodoma

□ In 2012- Ipinda – Kyela Mbeya

SUMMARY OF CLASSIFICATION PCR-CORRECTED

	N	Proportional	Lower 95% CI	Upper 95%CI
ETF	0	0.00	0.000	0.148
LCF	0	0.00	0.000	0.148
LPF	1	0.043	0.001	0.219
ACPR	22	0.957	0.781	0.999
Total	23			
WHT	2			
LCF	1	0.115		
Total	26			

SUMMARY OF CLASSIFICATION PCR-CORRECTED

	Number	Proportional	Lower 95% CI	Upper 95%CI
ETF	0	0.000	0.000	0.112
LCF	2	0.065	0.008	0.214
LPF	1	0.32	0.001	0.167
ACPR	28	0.903	0.742	0.980
	31			
WHT	3			
LCF	8	0.262		
Total	42			

Invivo 2012...

□ Butimba-Mwanza

SUMMARY OF CLASSIFICATION PCR-CORRECTED

	Number	Proportional	Lower 95% CI	Upper 95% CI
ETF	0	0.000	0.000	0.459
LCF	0	0.000	0.000	0.459
LPF	0	0.000	0.000	0.459
ACPR	6	1.000	0.541	1.000
Total	6			
WHT	0			
LCF	0	0.000		
Total	6			

□ Masasi-Mtwara

SUMMARY OF CLASSIFICATION PCR-CORRECTED

	Number	Proportional	Lower 95% CI	Upper 95% CI
ETF	0	0.000	0.000	0.074
LCF	0	0.000	0.000	0.074
LPF	0	0.000	0.000	0.074
ACPR	48	1.000	0.926	1.000
Total	48			
WHT	6			
LCF	22	0.368		
Total	76			

2012 - Summary findings...

- Efficacy at all sites was $>95\%$ except Kyela
- No early treatment failure
- Late parasitological failure
 - 6 patients
- Late clinical failure
 - 2 patients
- After PCR adjustment
 - 4 recrudescence
 - 3 new infections
 - 1 Negative PCR

General Summary of findings...

- Eight NMCP sites covered into two rounds
 - 2011-Ujiji-74, Kibaha-30, Mkuzi-32 and Mlimba-5
 - 2012-Chamwino -26,Kyela -44,-Nagaga 76 and Butimba-6
- In all sites the enrollment was below except Ujiji and Masasi
- Enrollment between Jun-October.
- Total of 293 children enrolled
 - With drawn 11
 - Lost to follow up 43
- 21 more withdrawn after PCR correction
 - New infections
 - Negative PCR
- 218 patients were analyzed.

Discussion and Conclusion

- Both ALu and ASAQ had very high efficacy
 - ▣ The clinical efficacy of ASAQ in previous studies eg. 2007 was relatively higher in areas with high transmission due to high rate of re-infections
- The lack of sufficient cases with malaria parasites was a major problem in both rounds
- New approaches are needed to capture more patients and reach the target sample size.

Way forward ...2014/2015

- Conduct a round of testing at 4 sites – from May 2014
 - ▣ Three ACTs to be tested – AL, ASAQ and DHA-PQ
- Future studies to include assessment of parasite clearance time to generate baseline data in Tanzania

Challenges for future studies

- Due to declining transmission, extending follow up to 6 months is needed
- Testing 2 ACTs per site

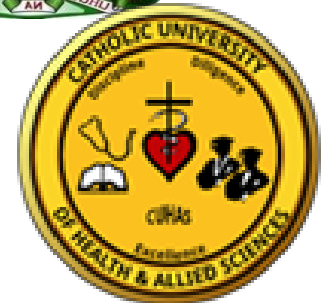
- **Finance:**
 - ▣ To extend the study to or beyond 6 months and
 - ▣ Testing 2 ACTs at each site
 - ▣ Surveillance of PCT (approx. USD120,000 per year)

Acknowledgements

- Partners



- Funders



- District Health Authorities

- Study Participants