The Potential and Complexity of Artemisia

by
Pierre LUTGEN, Ph.D. Luxembourg, lutgenp@gms.lu

Presentation made at WHO, Geneva, 25 January 2012, at 2d Nordic Malaria Conference 14 Sept 2012, at the Ministries of Health at Nairobi 26 Nov 2012 and Kampala Nov 28 2012, Lubumbashi, 25 May 2013

We first

1. retrieved in the scientific literature papers documenting the efficiency of *Artemisia annua* tea infusion
2. and then accumulated our own clinical trials and field experiences

The Vietcong lost more soldiers to malaria than to weapons.
Ho Chi Min turned to China for help.
Researchers at the Chinese Institute of Material Medicine found a region of China that reported no malaria cases,
and when they investigated, they discovered that its people drank a decoction of Artemesia annua at the first sign of malarial symptoms.

CJ Puotinen, NEHA Journal, Winter 2003

Pharmacology and Application of Chinese Materia Medica,
H Chang
World Scientific Publishing,
1986

Artemisia annua clinical studies

A 100% cure rate was achieved in 485 cases of vivax malaria treated with the tablet of dilute alcohol extract of the herb in doses spread over 3 days.

The current pharmacopeia of the People‘s Republic of China recommends 5 gr artemisia annua herbal drug in 1L/day for 5 days

C Debnath et al., J of the Korean Chem Soc. 55, 2011, 57-62

The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects.

Mueller MS, Karhagomba IB, Hirt HM, Wemakor E.

Hopital Nebobongo, Nebobongo, Congo. 2000

The plant Artemisia annua L. (Asteraceae) is listed in the Chinese pharmacopoeia as a remedy for various fevers including malaria, and contains the well-established antimalarial compound artemisinin. In this study, a hybrid form of A. annua was successfully cultivated in Central Africa. The aerial parts of the plant contained 0.63-0.70% artemisinin per dry weight, and approximately 40% of this artemisinin could be extracted by simple tea preparation methods. Five malaria patients who were treated with A. annua tea showed a rapid disappearance of parasitaemia within 2-4 days. An additional trial with 48 malaria patients showed a disappearance of parasitaemia in 44 patients (92%) within 4 days. Both trials showed a marked improvement of symptoms.

Results obtained by Anamed in 2000 in different locations of Zaïre

	Nebobongo	Bukavu/Lwiro	Kinshasa	Total
Number of patients	48	91	21	160
Negative parasitemia after 7 days	44 (92%)	86 (95%)	19 (91%)	149 (93%)

Regional health center Lwiro, Bukavu, 1999.

« 91 patients with positive plasmodium blood smears were treated with Artemisia annua tea for 5 days. After treatment 95% of the patients were free of parasites. »

www.sextocontinente.org/apoyohumano/a-a-anamed...

A proof-of-concept study, which commenced in June 2004 and ended in February this year, has yielded encouraging results. Clinical studies involving 48 patients with uncomplicated malaria have shown the whole-leaf drug to have impressive efficacy in treating the disease with no significant side effects.

Source: ‘New Agriculturist’ online , Naftali Kure , **Kenya**

COMPARATIVE STUDY OF THE QUALITY AND EFFICIENCY OF ARTEMISININ DRUG BASED AND ARTEMISIA ANNUA GROWN IN CAMEROON [MIM15225512]

Chougouo Kengne R.D., Kouamouo J*., Moyou Somo R**., Penge On'Okoko A***. *Université des Montagnes Cameroun ; ** IMPM /CRM et FMSB Cameroun ; *** Université de Kinshasa RDC.*

. In order to compare the antimalarial activity of artemisinin from Artemisia annua and other antimalarial drugs: artesunate and artesunate + amodiaquine in 3 villages from 2 regions (125 people). The results of the comparative study showed a significantly higher sensitivity of artemisia annua concoction (0 % of Echec Thérapeutique Tardif ETT) compared with that of artesunate (12.5% of ETT) and the artesunate combined with amodiaquine (14.30% of ETT).

The concoction intake for 7 days was 0% of ETT, significantly lower than that of 5 days intake (28.5%). The RTPA is above 80% for the 3 protocols indicating the absence of warning according to WHO criteria. The concoction of Artemisia annua is a good treatment of malaria seeing the results. To improve its effectiveness, it must be taken for at least 7 days or in combination with other antimalarial drugs.

MIM conference Nairobi, oct 2009

OPTIMIZING THE TREATMENT OF UNCOMPLICATED MALARIA USING TEA OF HYBRID *ARTEMISIA ANNUA*

Adelaide Bela Agostinho,
Ariadna Vlyalko,
João Massingarela and
João Fumane

Roma, 13th Mar 2009

On 160 volunteers in Mozambique

Summary of results (by PL)

- Average decrease of fever in 3 days for A annua tea and for artesunate-fansidar control
- Average decrease of parasitemia by 97 %in 3 days
- One or two cases of relapse
- TEA EQUIVALENT TO ACT

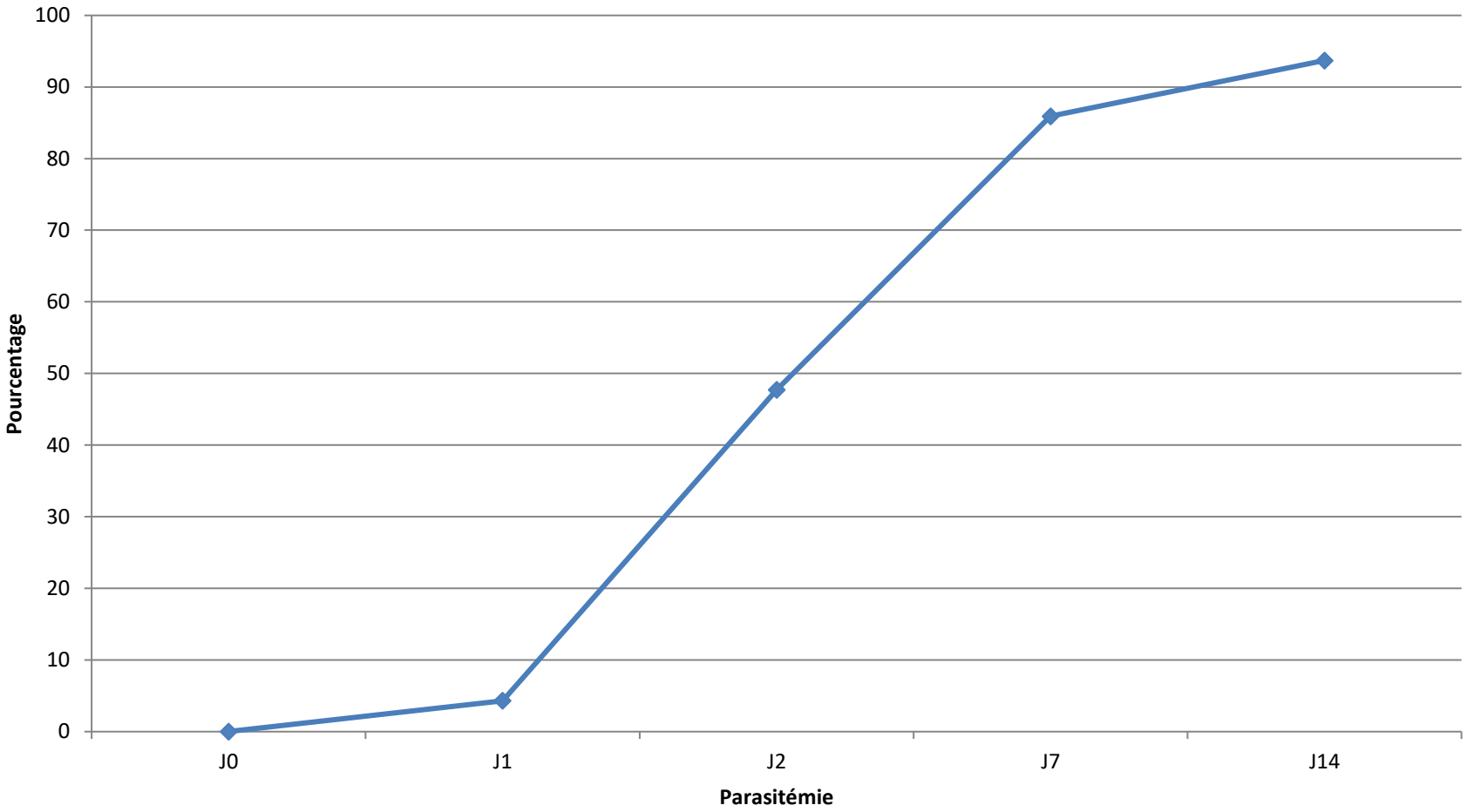
Ethiop. J. Health Biomed Sci., 2010. Vol.2, No.2

ORIGINAL ARTICLE

USE OF THE PLANT ARTEMISIA ANNUA AS A NATURAL ANTI-MALARIAL HERB IN ARBAMINCH TOWN

Gebeyaw Tiruneh[1], Yigzaw Kebede[2], Tegbar Yigzaw[3]*

Clinical trials, Dr E Fouda, Yaoundé, Cameroon, January 2010
74 patients (financed by LBMCC and IFBV Luxembourg)



Percentage of parasites eliminated in function of time

Merlin Willcox et al., Malaria Journal 2011, 10:84
Evaluation and pharmacovigilance of use….of Artemisia annua for malaria (in Kenya)

« **Overall the number of children treated was at least 250. They reported that all the children treated had recovered completely**”.

(Average artemisinin content of plants: 0.3%)

Trial done by medical doctors in India

Comparative study done in Two villages with MP positive cases

- **Jero Village (treated with AAA tea)**
- 35 Patients were given AAA tea for 7 days.
- All of them improved within 3 days of treatment except one child who did not take, died.
- Every one came back to their normal health within a few days.
- Test was done on 15/10/10

- **Dumiduar Village (treated with allopathy Medicine)**
- 20 Patients were treated with Chloroquine, primaquine & other antimalarials.
- Their improvement was quite slow and are still recovering to their normal health.
- Test was done on 15/10/10

Essais Artemisia annua de Luxembourg au dispensaire privé catholique de Dagana

Sœur Elke Steinacher
En collaboration avec Gembloux. U de Liège

La liste suivante reprend les noms des personnes atteintes du paludisme et soignées durant le mois de **septembre** 2011.

L'Artemisia a été tamisée et mélangée avec une pate arachide pour en enlever l'amertume. Par jour, 7g de poudre ont été ainsi administrés aux enfants et ceci durant 7 jours.
Des tests de TDR (Test Diagnostic Rapide) ont vérifié que les personnes étaient atteintes du palu et soignées à présent.

Nom	Age	Température C°	Etat
Sokhna Diara Sy	2 ans	38	guéri
Adéle Sene	11 ans	39	guéri
Fabine Sow	10 ans	37,8	guéri
Malick Sow	11 ans	38,3	guéri
Boubakar Khonte	9 ans	39	guéri
Aminata Niarem	9 ans	38,6	guéri
Melanmine Mane	12 ans	39,7	guéri
Moussa Fall	10 ans	38,8	guéri

De même un total de 34 enfants pour les mois de octobre et de novembre

Similar results are available from our partner Kachoré in Benin on 120 children

Results from Senegal on 70 patients during 3 months

GROUPE PRESENCE LOCALE

L'ESPOIR D'UN MONDE MEILLEUR

Birahim Ndiaye	8 ans	38,8	guéri
Soda Niasse	41ans	38,5	guéri
Abdoulaye Kassé	59ans	38,8	guéri
Ismaila Kane	70ans	38,6	guéri
Malamine Badji	57 ans	37,8	guéri
Coumba d Kébé	57 ans	38,3	guéri
Ndiathate Senghor	28ans	37,8	guéri
Anta Ndour	30ans	38,6	guéri
Tida Dramé	28 ans	39,7	guéri
Sokhna Coly	29 ans	38,8	guéri
Khadiatou Ba	36ans	37,8	statu quo
Siré Badji	15ans	38,3	guéri
Yacine Seck	18ans	38,6	guéri
Khady Thiam	22 ans	37,8	guéri
Amnata Sy	11ans	38,3	guéri
Cheikh Ba	34ans	37,3	guéri
Pape Diop	2ans	38,1	guéri

CHERS AMIS.

Community sensitization for the production and use of Artemisia tea in The Gambia

<u>Adults and children</u>

•35 people used as curing malaria using the 5g/liter@4 doses/day for 7 days (equals to 35g of dried leaf biomass)

•Recovery seen (72%) within 5 days & (98%) within 7 days

In fact the need to move to a treatment from 5 to 7 days is known since a long time

Il est recommandé de prolonger le traitement à l’artemisinine de 5 jours à 7 jours, afin de diminuer le pourcentage de rechutes précoces de
30-36 % à 10-20 %.

Vu Thi Phan, ex-directrice de l‘Institut national de Malariologie du Vietnam, 2002

British soldiers stationed in Macedonia taking oral quinine under the direct supervision of their commanding officer and sergeant Quinine's bitter taste and adverse events such as tinnitus resulted in highly disciplined drug administration being the only way to ensure soldiers took the drug. Photo reproduced from reference 7 with permission of the Imperial War Museum, London, Q32160.

CHIMIOSENSIBILITE *IN VITRO* DE *PLASMODIUM FALCIPARUM* PAR RAPPORT A LA TISANE *D'ARTEMISIA ANNUA*
ET ACTION STERILISANTE DE LA MEME TISANE SUR LES EAUX POLLUEES

Thèse de doctorat de Omar Gueye financée par
ArcelorMittalFoundation et IFBV

"En conclusion les tests *ex vivo** sur les souches de P. falciparum montrent que la tisane luxembourgeoise serait efficace. Cette efficacité démontrée contre P. falciparum, malgré une teneur en artémisinine faible, nécessite des études plus approfondies qui vont surtout porter sur la concentration des autres substances (polyphénols, huiles essentielles, polysaccharides, scopoletine....) sur les lymphocytes, le système immunitaire..."

* DELI test sur 57 échantillons sanguins de personnes infectées

Vol. 7(7), pp. 107-113, August 2013

African Journal of Biochemistry Research

Tea *Artemisia annua* inhibits *Plasmodium falciparum* isolates collected in Pikine, Senegal

Gueye Papa El hadji Omar, …Lutgen Pierre

Concernant les études faites, je pars au Bénin le 13 janvier et espère avoir des résultats plus officiels,
mais pour le moment, ceux obtenus avec la tisane (en curatif) sont assez concluants. Avec l'extrait brut,
le nombre de patients n'est pas encore suffisant pour pouvoir donner un résultat fiable.

Joëlle Leclercq
UCL
2012

GROUPE PRESENCE LOCALE

L'ESPOIR D'UN MONDE MEILLEUR

Birahim Ndiaye	8 ans	38,8	guéri
Soda Niasse	41ans	38,5	guéri
Abdoulaye Kassé	59ans	38,8	guéri
Ismaila Kane	70ans	38,6	guéri
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Amnata Sy	11ans	38,3	guéri
Cheikh Ba	34ans	37,3	guéri
Pape Diop	2ans	38,1	guéri

CHERS AMIS.

Trials with 500 mg tablets of Artemisia annua leaf powder in Kenya 2005 on **48** patients at different doses over 6 days (total artemisinin in doses ranging from 60 to 210 mg in 6 days).

Only 3 cases of recrudescence on day 14.

Ahmed Hassanali, ICIPE

Le Dr Yves Saint Hillier de Besançon a fabriqué 20 000 gélules contenant pour les plus gros 1 gr de poudre d'artemisia annua moulue

Aucun échec thérapeutique ou effet négatif n'a été rapporté pour les essais qu'il a fait sur des centaines d'adultes et d'enfants au Mali. Ils permettent l'application rectale en cas de malaria sévère. Les résultats étaient spectaculaires chez les enfants

Gélules-Capsules

Hannelore Klabes also uses capsules in Burundi and received the Bundesverdienstkreuz for this

Wan YE and Zang QZ had already made similar gelatin capsules in **1992** : 100 % cure rate for plasmodium vivax

The Surprising Efficiency of Artemisia annua Powder Capsules

Michel Onimus,… and Pierre Lutgen

Medicinal and Aromatic Plants, 2013 , 2-3.

Michel Onimus, surgeon in pediatric orthopedics, has often been confronted with severe malaria resurgence in children after surgical interventions in the Central African Republic. Based on the positive results obtained in other countries (China, Mali, Tanzania, RDCongo..) by other partners with capsules containing Artemisia annua leaf powder, he made a trial with these capsules on 25 patients on the day before and after the surgery (total 50 hours on average), and obtained very encouraging results. The quantities of artemisia powder used are less than 1 gram per child. His claim that a treatment of 7 days with these capsules would have eliminated parasitemia completely is correct in our opinion, based on our own clinical trials. And we also support his claim that Artemisia annua powder (totum) is superior to infusions or extracts.

Please note also the analgesic effect noticed. This effect has been described for other artemisia species in the scientific literature. Interesting for poor people who cannot afford expensive antinociceptive drugs.

Interesting is also his anecdotical observation on 5 malaria patients where Malarone and ACTs had failed and which were cured after 7 days artemisia capsule treatment.

RD Congo 2012.

54 volunteers suffering from malaria were treated during 10 days with decreasing doses of capsules containing powdered leaves of *Artemisia annua*. All were free of fever after 2 days and 51 were free of parasites after 10 days. The total amount of dried herb administered per patient was 15 gr and the total amount of artemisinin contained in these was 15 mg.

Ou encore la poudre finement moulue de l’herbe sèche mélangée à du Mbouraké au Sénégal: beurre d’arachide, sucre, jus de citron

Based on the medical records of over **48,000** women treated over a period of more than 20 years
the team at the Shoklo Malaria Research Unit at the Thai-Burma border concludes

t

The study provides a level of reassurance regarding the potential risk associated with artemisinin exposure in early pregnancy, compared with the established risk of malaria

http://www.shoklo-unit.com/

What we have learned so far

Tea of *Artemisia annua*

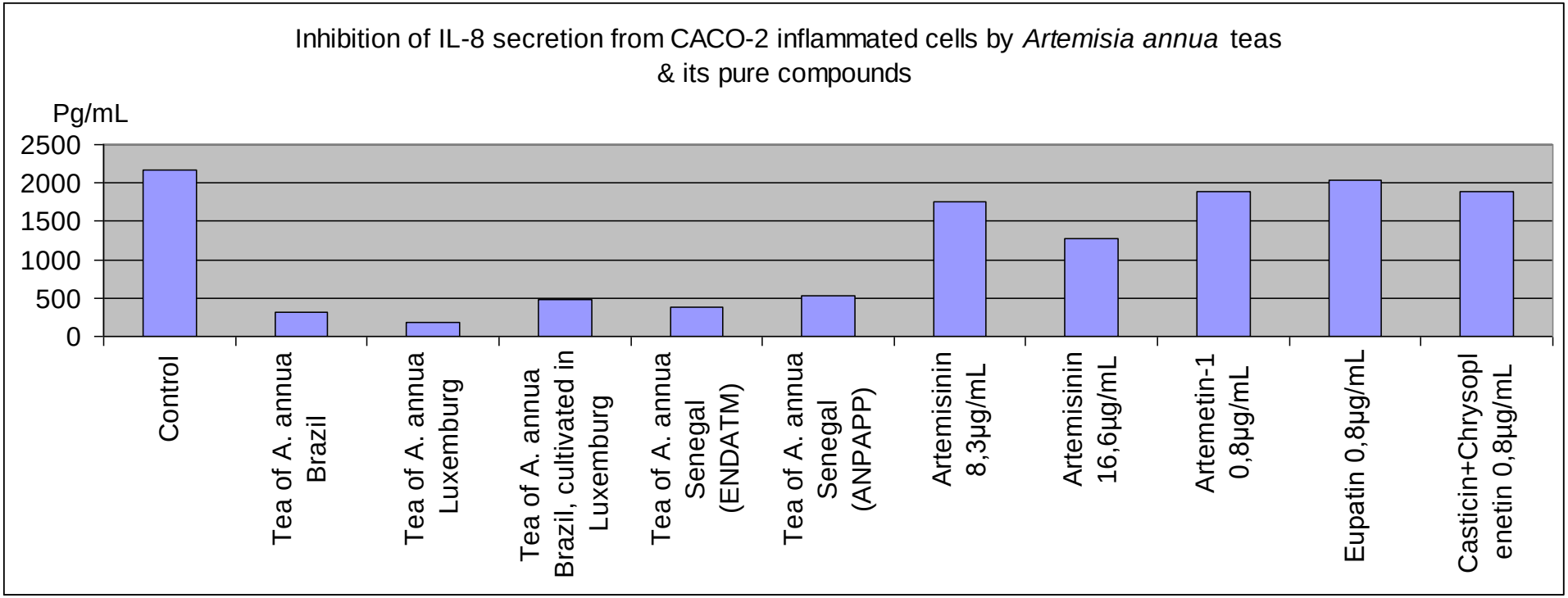
- Efficiency >95%
- No side effects*
- Low cost
- No resistance shown up til today

* Artemisia annua and artemisinin are not toxic.
Review of 108 studies on 9241 patients
Ribiero et al, Med Trop 1998.

Quelques faits intrigants notés au cours des dernières années

Anti-inflammatory effect on CACO-2

P de Magalhaes, UCL, 2009



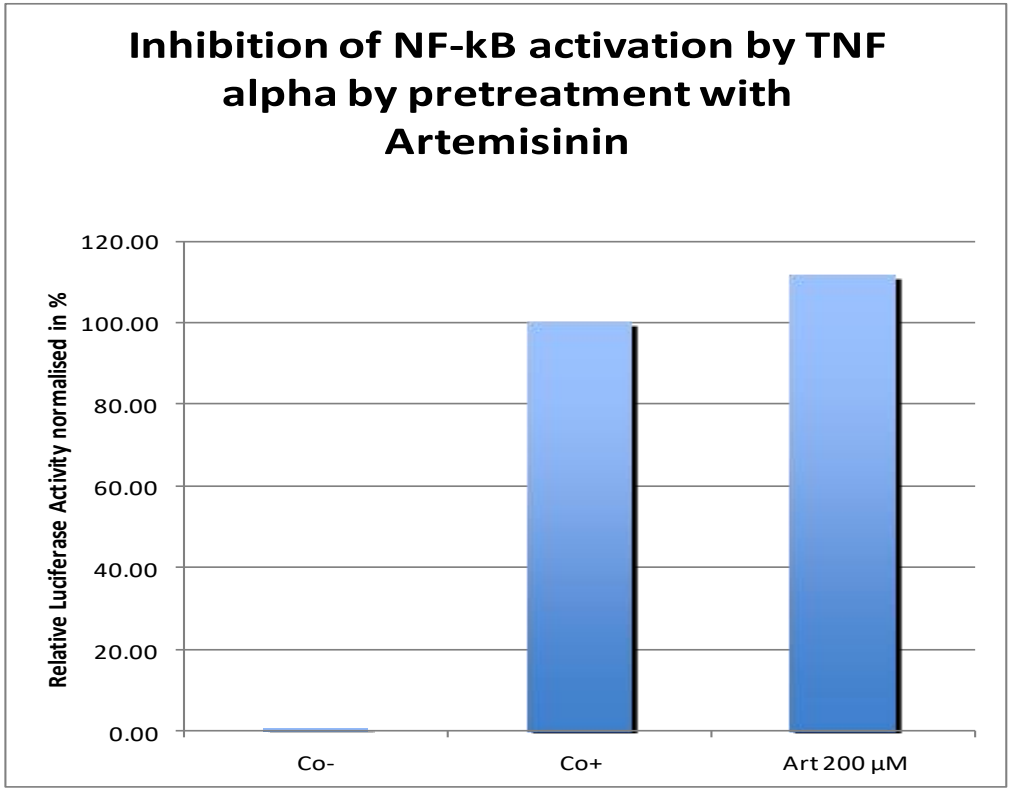
Why would the tea from Luxembourg be different or even better ?

Cholesterol is food for plasmodium.

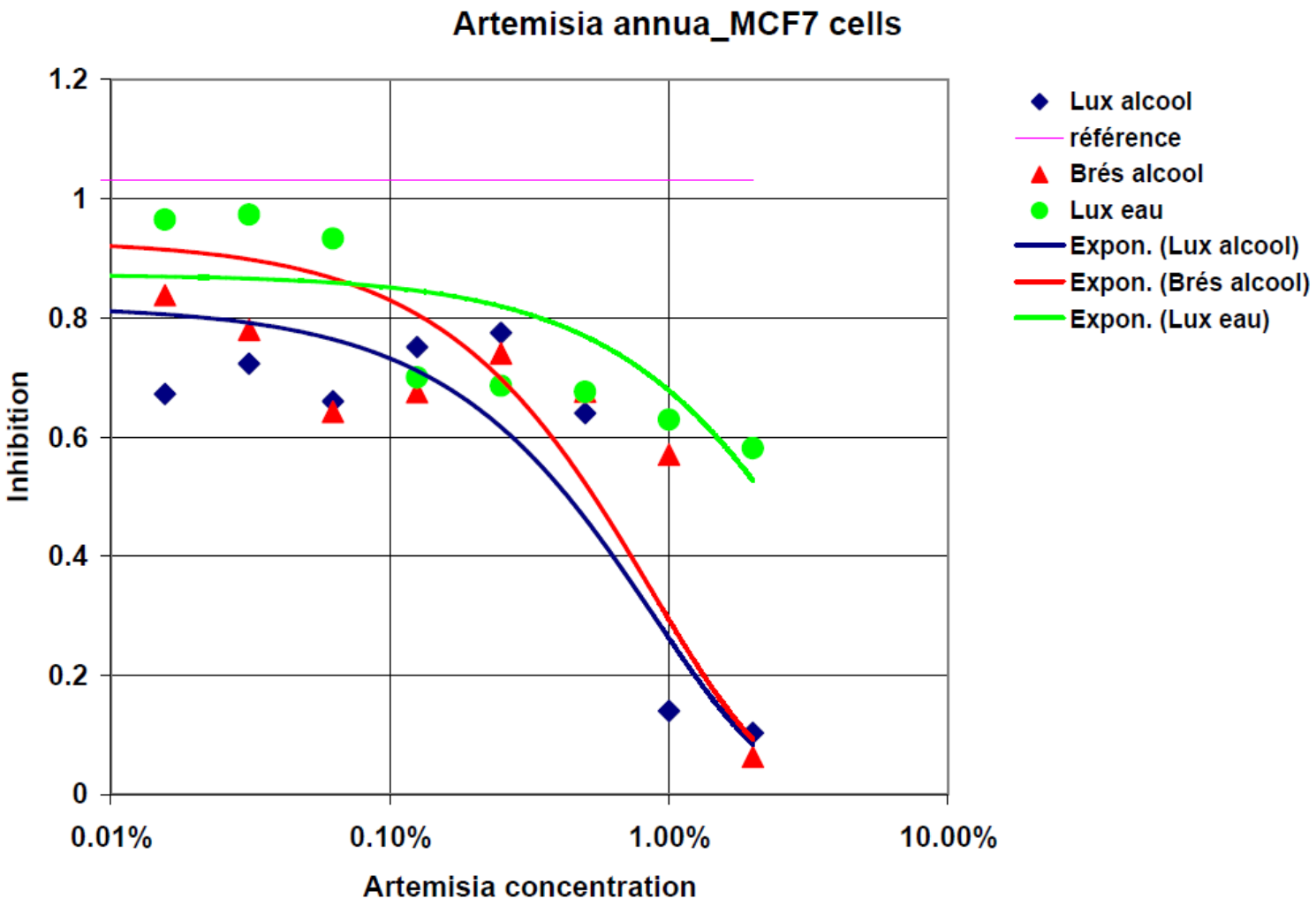
Artemisia plants have a cholesterol lowering effect because they contain high concentration of phytosterols

Pure artemisinine is pro-inflammatory and immuno-depressive

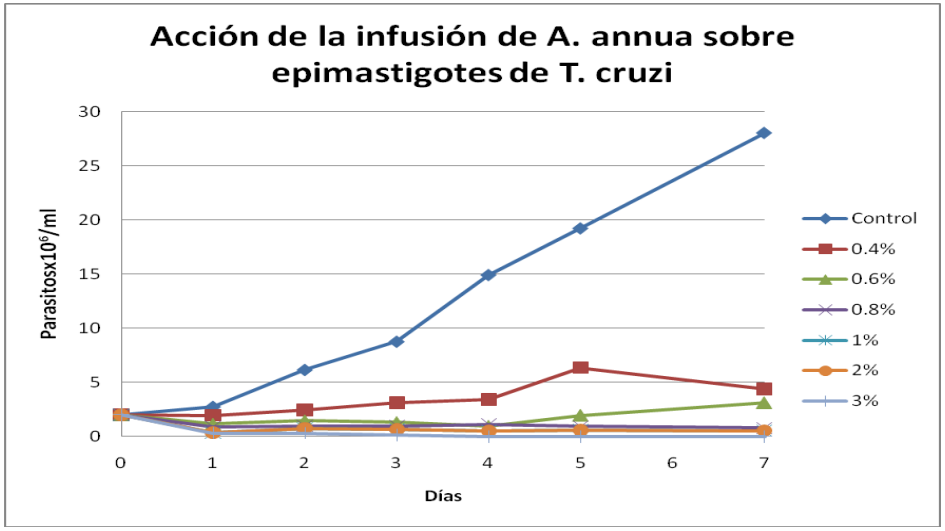
Results from LBMCC, Luxembourg



Up to now our analysis showed that artemisinin is definitely not responsible for the antiHIV activity
Fr. Van der Kooy, Leiden, personal communication

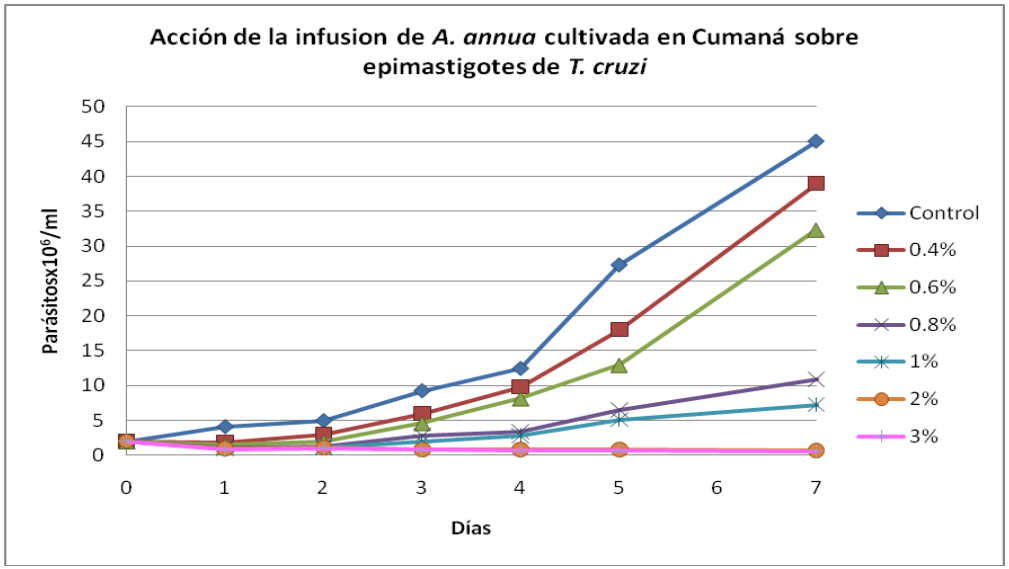


Cytotoxicity test run by the CRP-Santé at Luxembourg (Dr Ning Wang) showing that the tea from Luxembourg is equivalent to the tea of Brazil



Universidad de Cumana, Venezuela, Dr Berizbeitia

Tea from Luxembourg



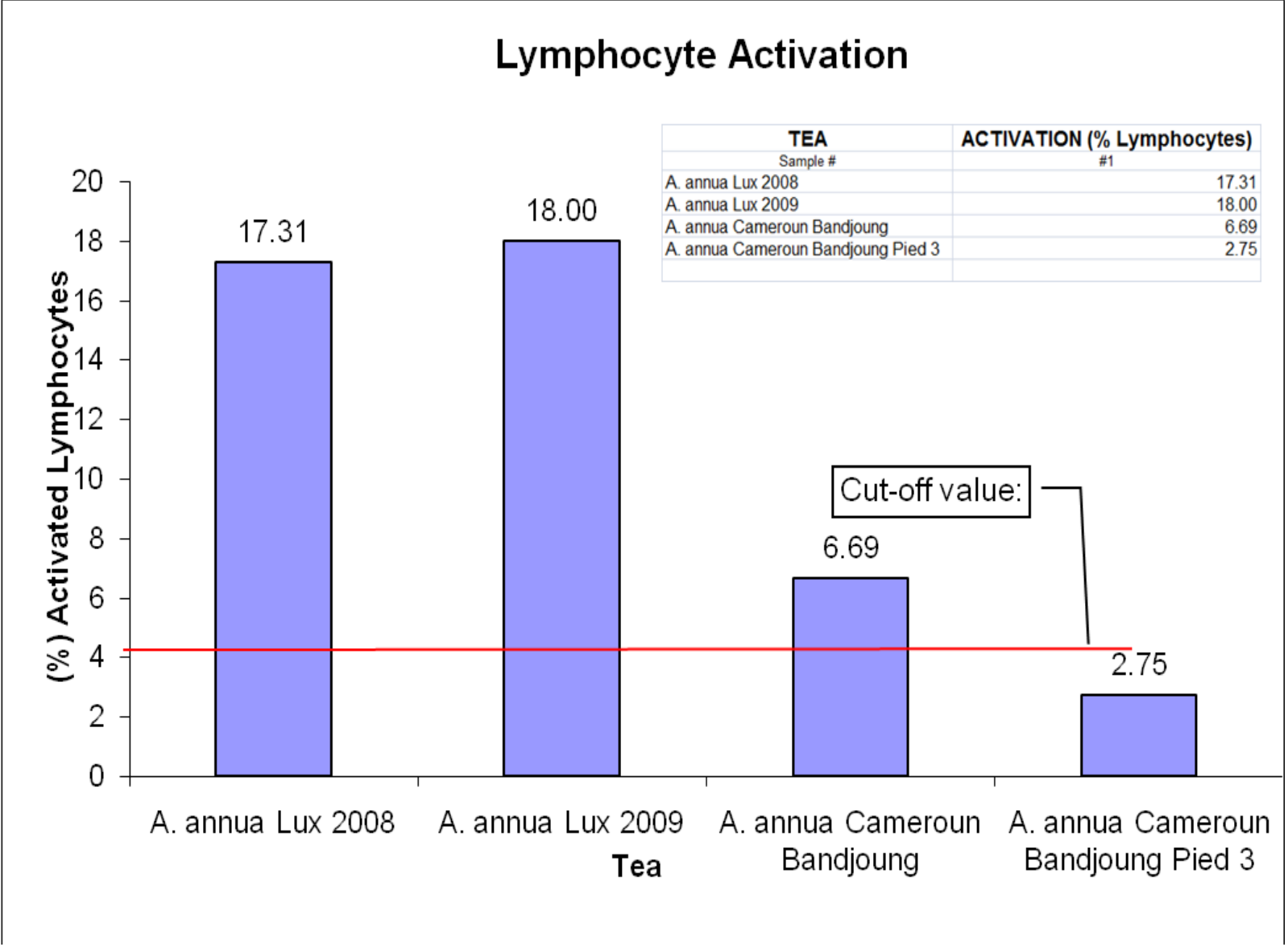
Tea from Venezuela

UNIVERSIDAD DE ANTIOQUIA
1803

Leishmaniose

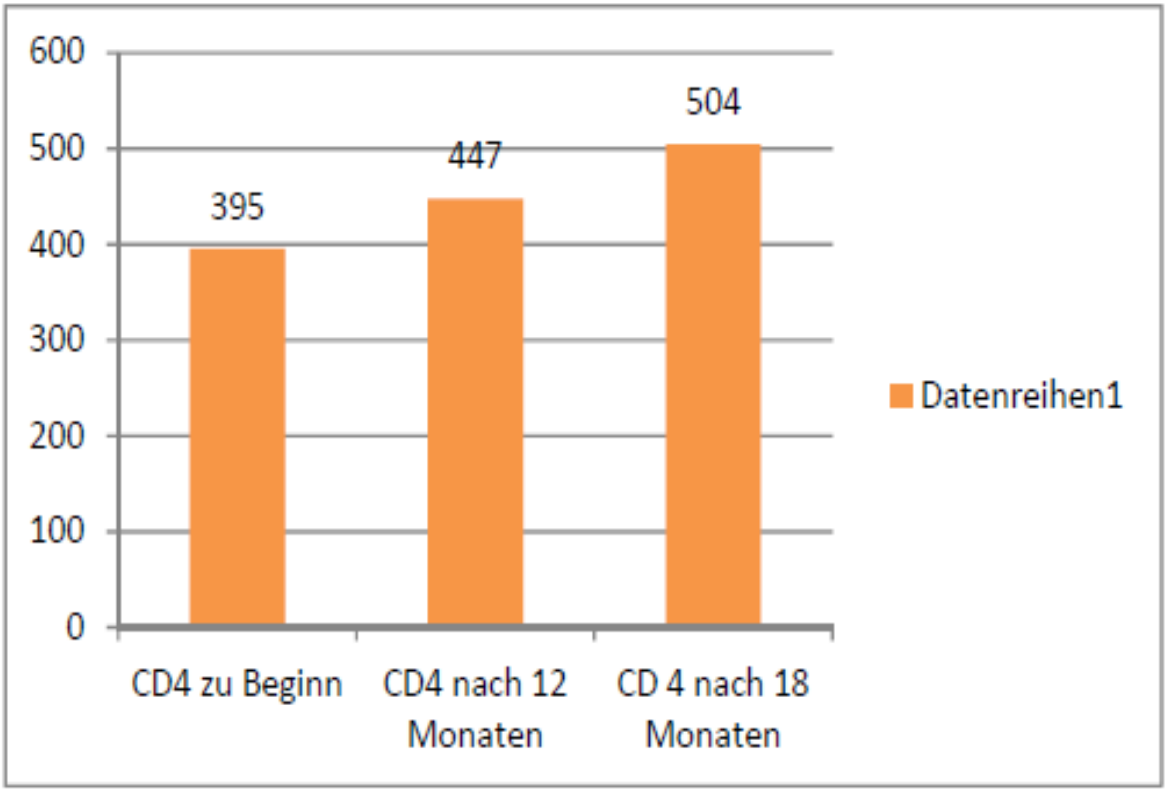
La tisane d'artemisia annua luxembourgeoise administrée par voie orale à une dose
de 100 mg par kg de poids corporel pendant 20 jours conduit à une guérison de 100% telle que mise en évidence par une cicatrisation totale des ulcères chez les hamsters infectés.

Dr Ivan Velez
PECET
Expert OMS Genève pour la Leishmaniose
15 Aug 2010



TEA	ACTIVATION (% Lymphocytes)
Sample #	#1
A. annua Lux 2008	17.31
A. annua Lux 2009	18.00
A. annua Cameroun Bandjoung	6.69
A. annua Cameroun Bandjoung Pied 3	2.75

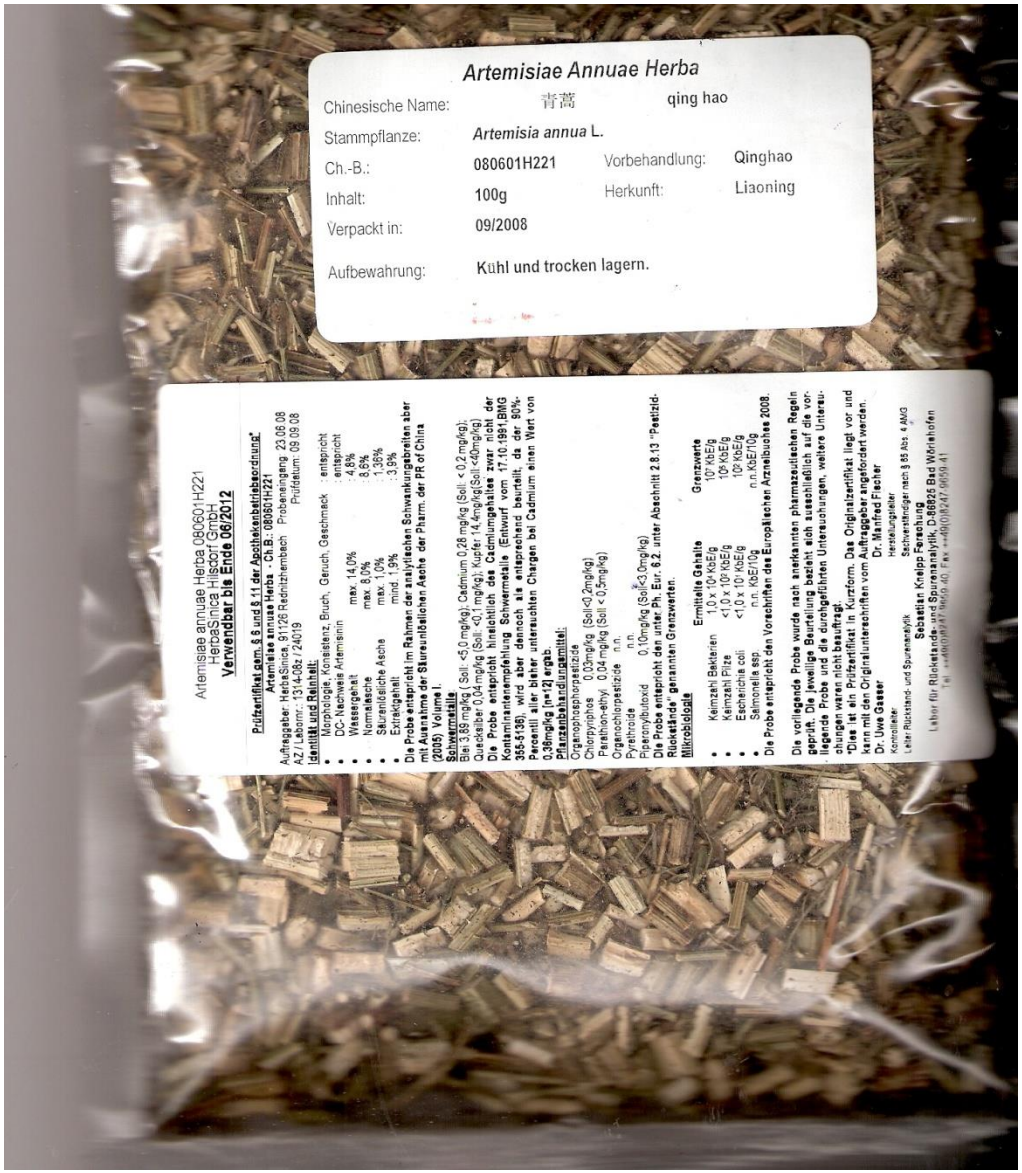
J.M.Michels and P. Lutgen, Luxembourg,2010, unpublished



Anstieg des mittleren CD 4 Wertes bei 15 Patienten

CD4 increase after regular consumption of A annua tea during several months

Personal commication from F Roelofsen



Tea of Chinese origin sold in Luxembourg contains a lot of stems rich in scopoletin

Artemisia is a unique plant which contains **sulfated polysaccharids** which

- Reduce the mobility of sporozoites interferering with CS
- Prevent the sporozoites injected by the mosquito to enter the liver
- and the erythrocytes by a heparan sulfate interference
- Reduce the concentration of glucose in the blood, starving thus plasmodia
- Prolongate dormancy

Malaria can be eradicated ba artemisia annua tea in a few years as shown in Ugandan villages (P.E, Ogwang, Ministry of Health, Kampala)

Artemisia annua also has strong **gametocytocidal** properties, inhibiting thus the transmission from man to mosquito (WHO/MAL/98.1086).

It stimulates the immune system and drinking a few cups per week prevents the malaria infection as it was demonstrated in 80 schools in **Kenya** and for 2000 farmers in **Uganda** in 2011.

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An African “vaccine” against malaria

Since 12 months a product is available in the pharmacies of Uganda. The product has been released after clinical and community trials over 3 years which have demonstrated that if taken regularly during one year it renders a person immune against malaria. The product called ARTAVOL® is composed of ground kernels of avocado, extracts of lemon grass and extracts of dried artemisia It is sold in tins of 100 gr and has the appearance of Nescafé granules.

ARTAVOL® was developed by scientists at Makerere University. The R&D was supported by Government of Uganda

In Uganda for improved health effect of the *artemisia annua* they remove the artemisinin from the infusion.

In China, some 2000 years ago, it was claimed that *artemisia apiacea* (containing no artemisinin) was better than *artemisia annua*.

In South Africa *artemisia afra*, not containing artemisinin either, is a strong antimalarial

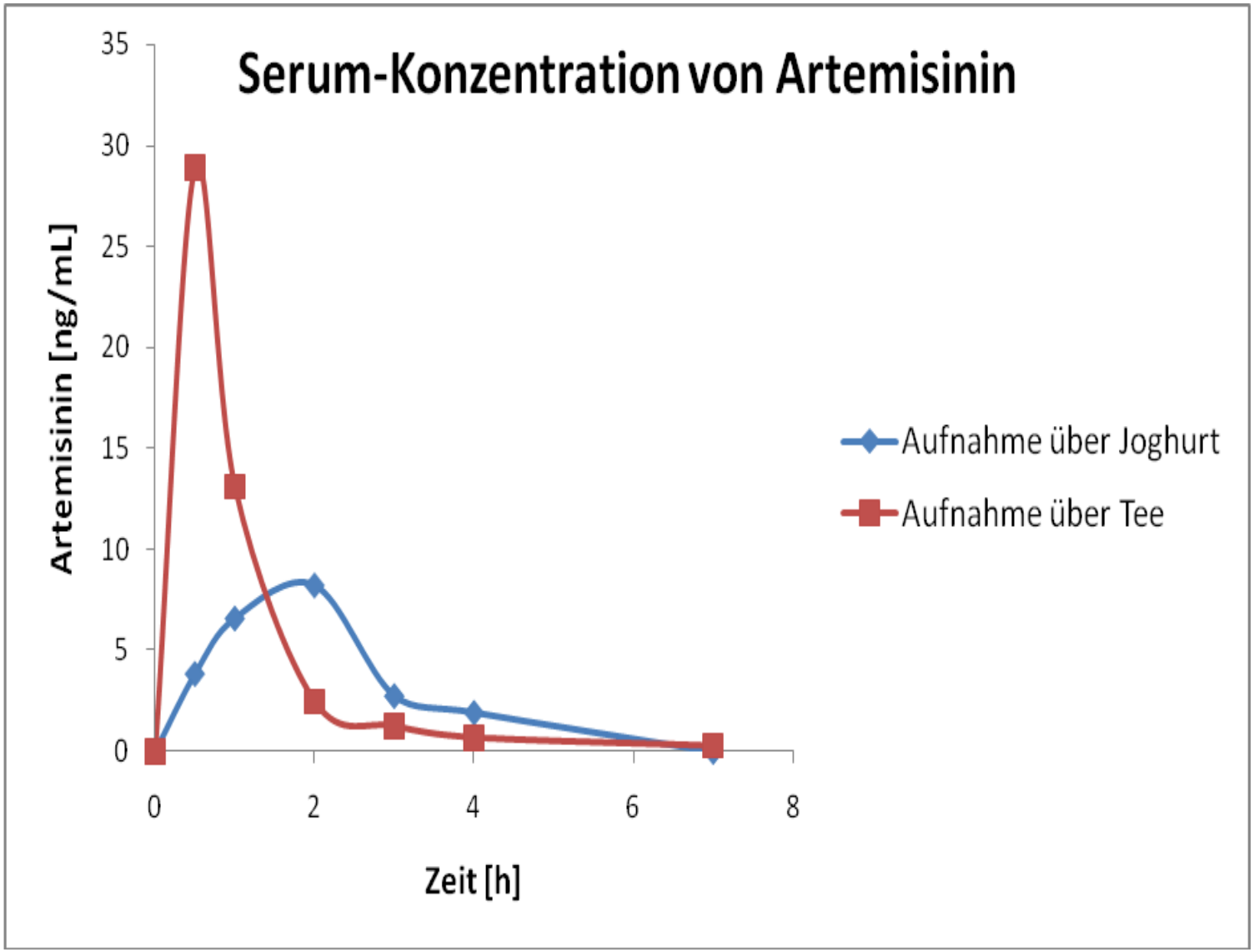
We have many anecdoctical reports indicating that taking any antimalarial (lumefantrine, quinine, artemisinine) with fat (arachid oil, porridge, palm oil, yoghurt) increases its therapeutic power

Recent findings of Dr Felicitas Roelofsen in India
(personal communication)

Concentrations of artemisinin in the blood when drinking *artemisia annua* tea

On day 1:	27 ng/ml
On day 7:	8 ng/ml
On day 14:	4 ng/ml

On day 21: 28 ng/ml if between day 14 and 21 you had no tea consumption


Serum-Konzentration von Artemisinin
Artemisinin [ng/mL]
35
30
25
20
15
10
5
0
0
2
4
6
8
Zeit [h]
Aufnahme über Joghurt
Aufnahme über Tee

Synergy olive oil and artemisinin

B Isacchi, Uni Firenze

50 µg/ml Olive Leaf Extract = 12% reduction of parasitemia
10 µg/ml Olive Leaf Extract = no reduction

40 nM ART=100% reduction of parasitemia
40 nM ART+50 µg/ml OLE =100% reduction of parasitemia
40 nM ART+10 µg/ml OLE =100% reduction of parasitemia

20 nM ART=73% reduction of parasitemia
20 nM ART+ 50 µg/ml OLE =90% reduction of parasitemia
20 nM ART+ 10 µg/ml OLE =75% reduction of parasitemia

10 nM ART=37% reduction of parasitemia
10 nM ART+ 50 µg/ml OLE =69% reduction of parasitemia
10 nM ART+ 10 µg/ml OLE =35% reduction of parasitemia

5 nM ART=24% reduction of parasitemia
5 nM ART+ 50 µg/ml OLE =48% reduction of parasitemia
5 nM ART+ 10 µg/ml OLE =27% reduction of parasitemia

2.5 nM ART=17% reduction of parasitemia
2.5 nM ART+ 50 µg/ml OLE =34% reduction of parasitemia
2.5 nM ART+ 10 µg/ml OLE =15% reduction of parasitemia

1.25 nM ART=13% reduction of parasitemia
1.25 nM ART+ 50 µg/ml OLE =27% reduction of parasitemia
1.25 nM ART+ 10 µg/ml OLE =11% reduction of parasitemia

0.625 nM ART=4% reduction of parasitemia
0.625 nM ART+ 50 µg/ml OLE =19% reduction of parasitemia
0.625 nM ART+ 10 µg/ml OLE =3% reduction of parasitemia

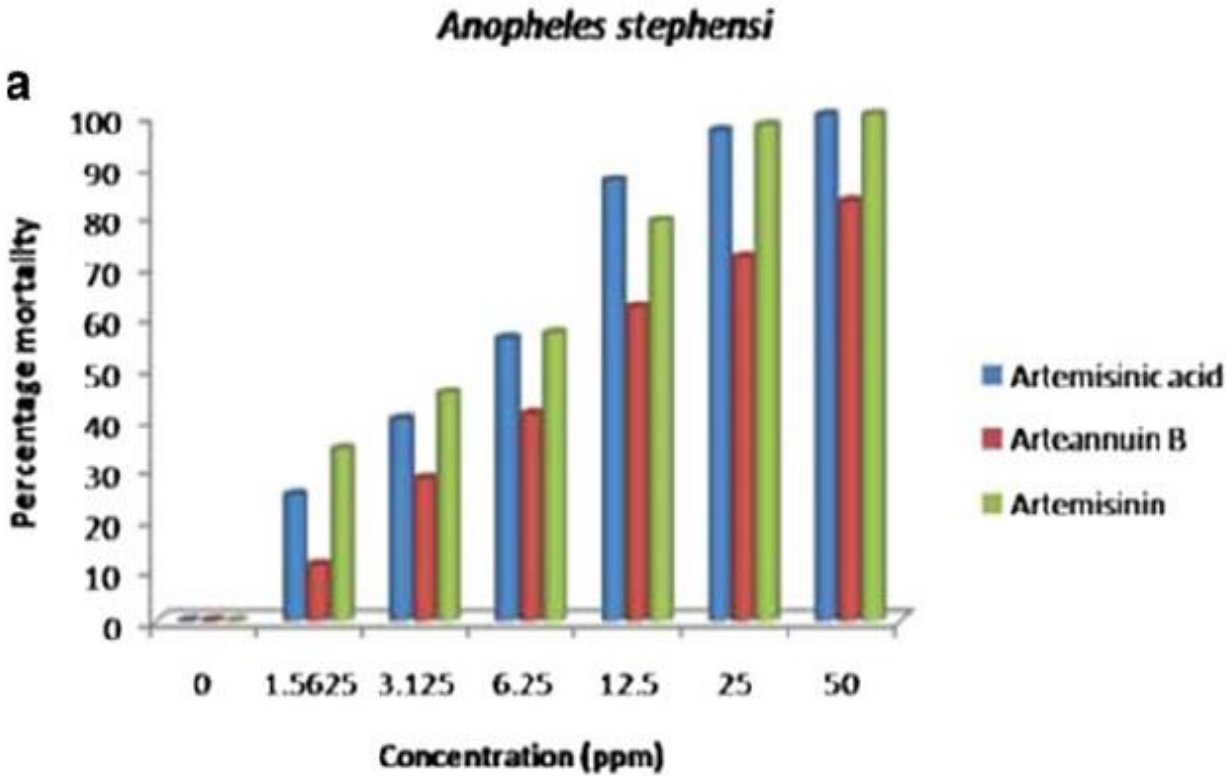
Applying the Avogadro number: in any artemisia plant there are billions and billions of molecules of artemisinin ready to attack each plasmodium

There are two genotypes of Artemisia annua

a. Rich in artemisinin and camphor

b. Rich in arteannuin-B and artemisia ketone

It appears that these two molecules are strong antimalarials: there role has been ignored,
a new research field



Larvicidal properties malaria and dengue
G Sharma, Parasitol Res 25 Oct 2013

Confirm the data of T Efferth, Phytomedicine, 2011 that the cytotoxicity of arteannuin-B against 5 different cancer cells is equivalent to that of artemisinin

Limonene Arrests Parasite Development and Inhibits Isoprenylation of Proteins in *Plasmodium falciparum*

Ivan Cruz Moura, Gerhard Wunderlich, [...], and Emília A. Kimura
Antimicrob Agents Chemother. 2001 September; 45(9): 2553–2558.

Limonene, 1.8 cineol and the precursors arteannuin-B and artemisitene have cytotoxic effects on cancer cells similar to those of artemisisin

T.Efferth et al., Phytomedicine, 18. 2011. University of Mainz

British Journal of Pharmacology and Toxicology 4(3): 89-94, 2013

Antibacterial and Antifungal Activity of the Essential Oil Extracted by Hydro-Distillation from *Artemisia annua* Grown in West-Cameroon [1]

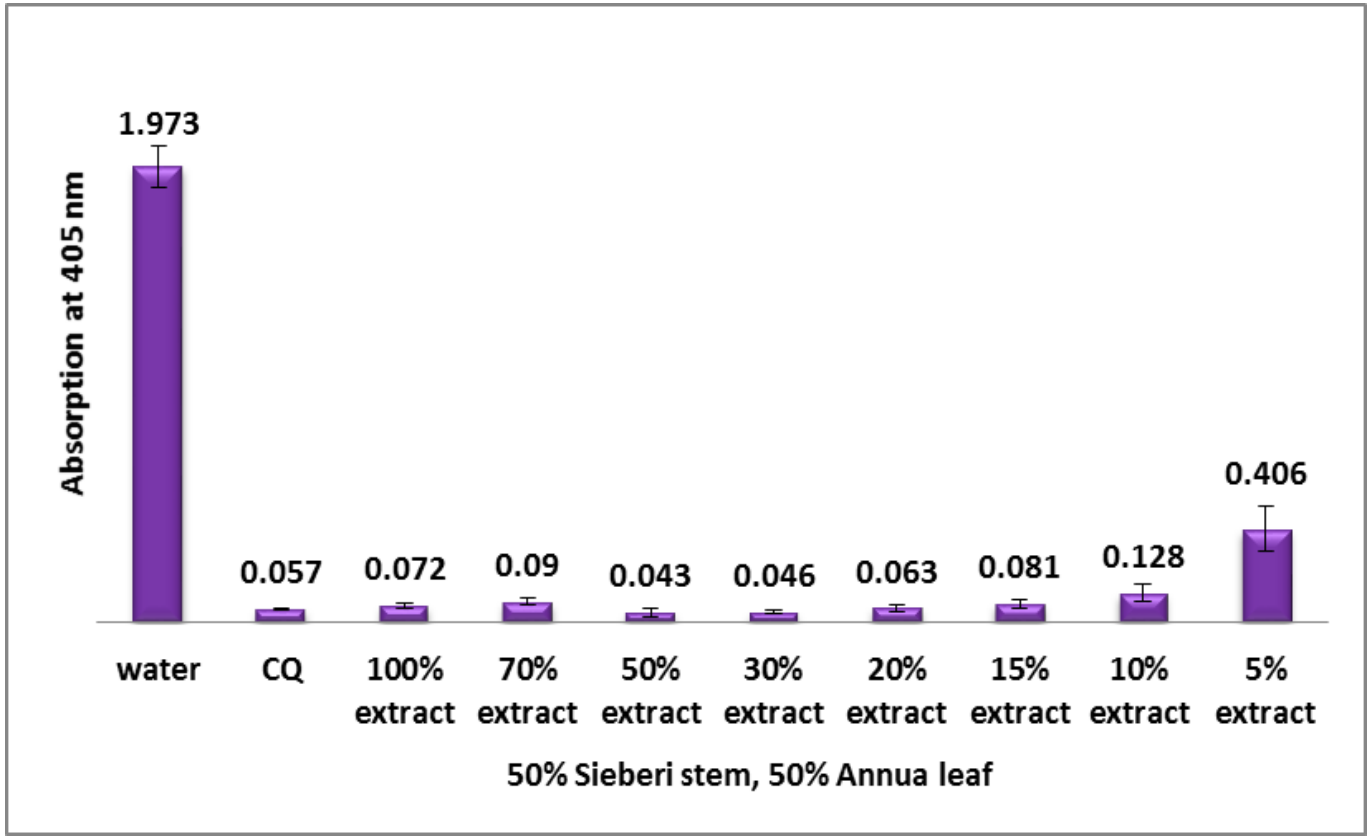
Chougouo Kengne Rosine Désirée

Also against Cholera

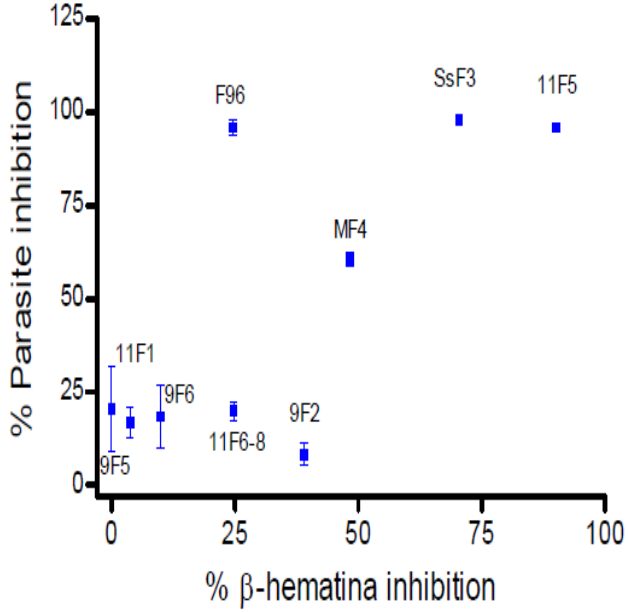
Investigations of *Artemisia annua* & *Artemesia sieberi* water extracts inhibitory effects on β-hematin formation

Mutaz Akkawi[1], Suhair Jaber [..] & Pierre Lutgen[2]

1.Al-Quds University,West Bank, Palestine
2. IFBV-BELHERB, Luxembourg,



Column diagram representing the potential anti-malarial activity of 50% mixture of Artemisia sieberi stem and 50% Artemisia annua leaf, water extract using compared to the negative and positive control: CQ-chloroquine 0.1mg/ml showing the absorption values of dissolved β-hematin The absorption is inversely proportional to drugs efficiency, the lower the absorption is, the drug is considered to be more efficient.



Graphic 1. Pearson Correlation test between inhibition of β-hematin formation and antiplasmodial activity

Table 2. Antiplasmodial activityIC_{50} (μg/mL) and Citotoxicity U937 IC_{50} (μg/mL)

Culture of *Artemisia annua*
at Walferdange-L to be packed at "Téi vum Séi"

We have plantations in a dozen countries and reach in a few regions a production volume which requires the implementation of a distribution and marketing system (FANGA project)

Our objective: see artemisia growing in every African garden

In Luxembourg, in addition to Artemisia annua from different origins we also now have small plantations of:

- Artemisia apicaea
- Artemisia afra
- Artemisia pontica
- Artemisia herba alba (sieberi)
- Artemisia abrotanum
- Artemisia absinthium
- Artemisia vulgaris

All have official LUX herbarium numbers

IFBV has developed a worlwide partnership

Belherb (Association for the promotion of herbal medicine) from Belgium-Luxembourg is a group of 10 doctors and university researchers

who closely work with universities in Senegal, Benin, Gambia, Kenya, Uganda, Cameroon, Congo, Central-Africa, Colombia, Brazil, Venezuela, Perou

And numerous associations in the North and the South

Artemisia annua plants around a house or a school are an excellent repellent for mosquitoes.

Also burning the dry herb in a dormitory.

Concerns raised by ACTs

J.Clin.Microbiol 2007 August 45(8): 2734-2736

Shelf life of Predosed Plates Containing Mefloquine,Artemisinin, and Artesunate

S.Houzé et al., Laboratoire de Parasitologie, Paris

The shelf lives of preserved antimalarial agent-predosed plates according to the type of wrapping and the temperature of storage were studied by measuring the 50% inhibitory concentrations of drug for *Plasmodium falciparum* 3D7. The shelf life of mefloquine was 8 weeks at 25° C; and those of artesunate, artemisinin, and dihydroartemisinin were a minimum of 24, 12, and 8 weeks, respectively, at 4° C.

At 37° C, whatever the conditions of packaging or the drug used, the plates were no longer valid after 1 week.

The artemisia annua herb however conserves its properties for many years if stored in dry ventilated area

50 % of ACT pills sold on the market are counterfeit.
A crime and a disaster.

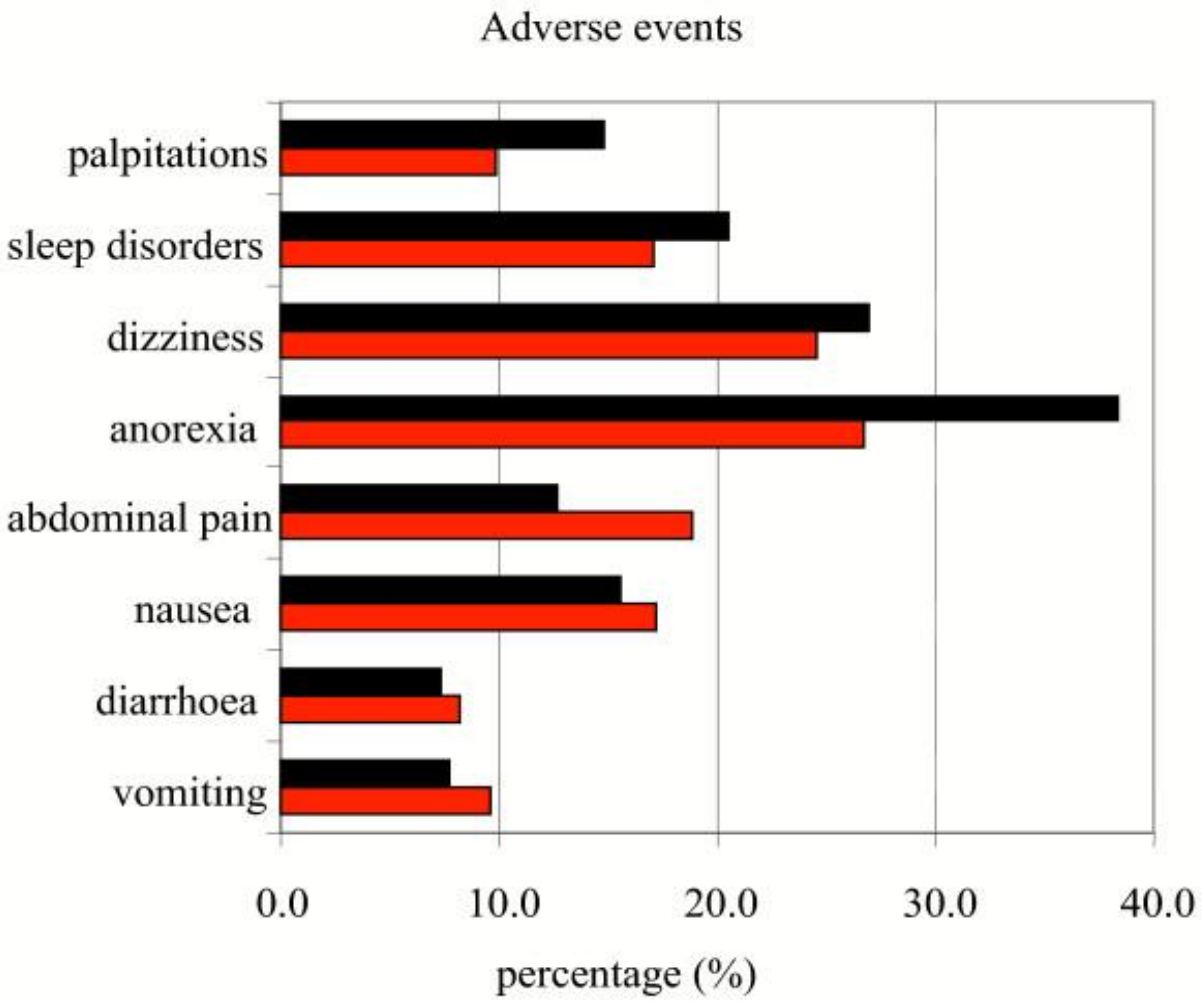
Newton PN, et al. (2006) Manslaughter by Fake Artesunate in Asia—

Will Africa Be Next? PLoS Med 3(6):

Genuine (left), Counterfeit (right). Artesunate, Cameroon.

Artemisia annua tea never caused side effects, ACTs do (red: lumefantrine, black mefloquine)

R.Hutagalung et al., Malaria Journal, 4, 48, 2005



All these negative side effects may lead to non compliance with drug administration and consequently to resistance

Malar J. 2011 Mar 8;10:56.

Artemisinin-induced parasite dormancy: a plausible mechanism for treatment failure.

Codd A,

But a new research field has opened: Certain polysaccharides or peptidoglucans prevent excystement of dormant plasmodia.

Hepatotoxic and hemolytic effects of acute exposure of rats to artesunate

Omotuyi, I. O. et al . Afr J Bioch Res, May 2008

At doses which are lower than those prescribed by WHO/MAL/98.1086 : 20 mg/kg as loading dose followed by 10 mg/kg for 6 consecutive days

In African countries the access to ACTs remains low: 3%

0.1 % in Gambie to 13 % in Zambia.

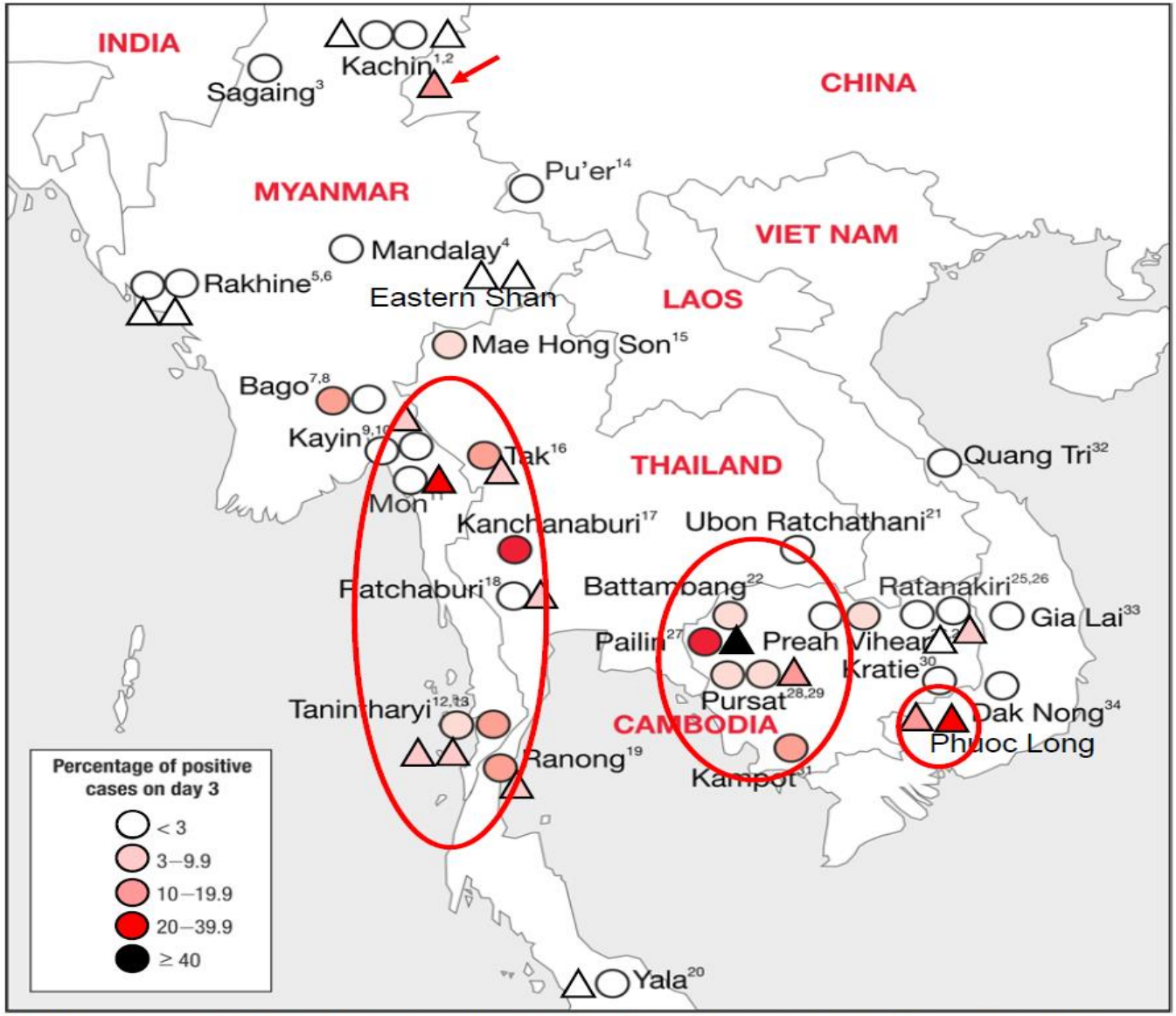
World Malaria Report . Sept 2008

In several countries resistance to artesunate or artemether has developed.
Of major concern to WHO and MSF

World Health Organization

GLOBAL MALARIA PROGRAMME

Figure. Percentage of positive cases on day 3 after ACT



Circles represent data before November 2010 and triangles data after November 2011.

Resistance to ACTs, not only in Asia but also in Africa

Persistent detection of Plasmodium falciparum, …….after ACT treatment of Ghanaian school-children

B Dinko et al.
Int J Parasitol, 2013, 3, 45-50)

In a double-blind controlled trial in The Gambia on 14017 individuals with a placebo and SP-artesunate, no benefit was seen for this MDA – mass drug administration. The malaria incidence even became higher in the treated group.

L Von Seidlein et al.,, Trans Royal Society of Trop Med 2003, 97, 217-225

Residual P. falciparum parasitemia in Kenyan children after ACT therapy …

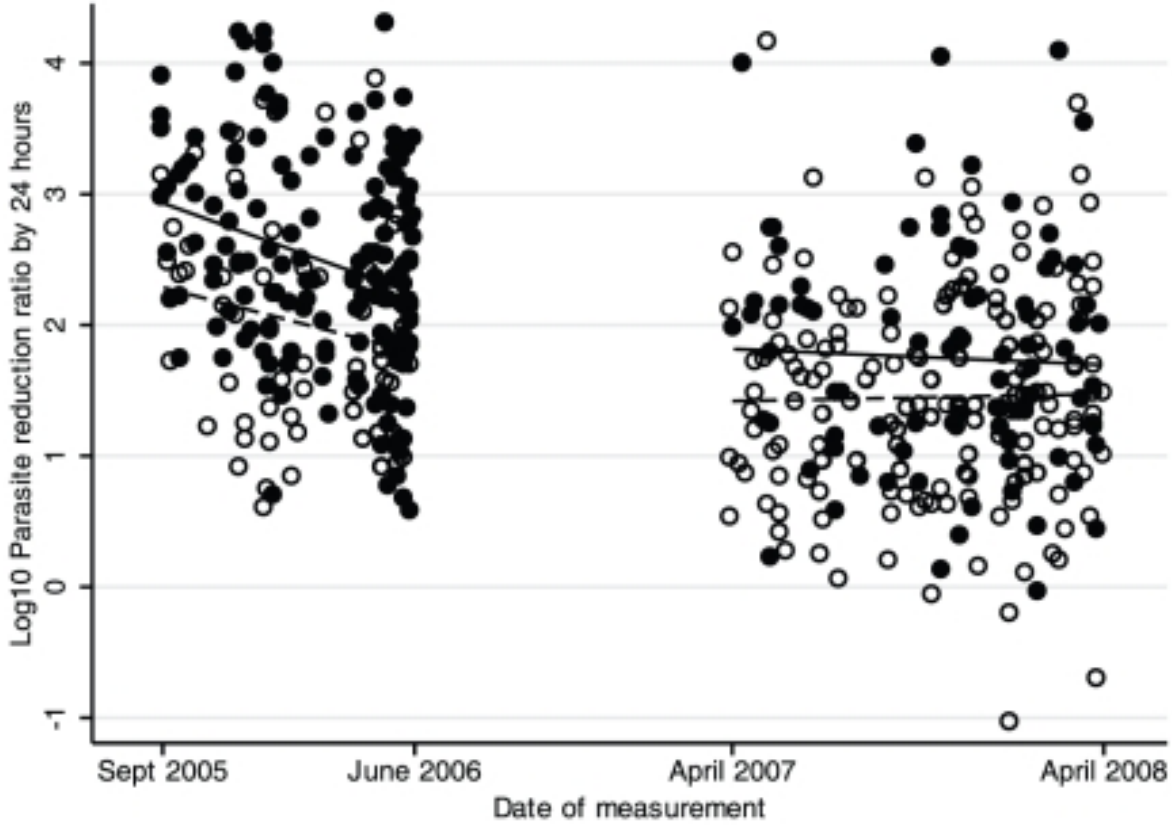
KB Beshir et al., J Infect Dis. September 4, 2013.

At Kilifi, Kenya 20 parasitological failures on day 42 for treatment of 74 persons with Coartem

KEMRI-Wellcome Trust Research programme, 2006

In Kenya declining responsiveness to ACTs on 474 children

S Borrmann et al., PlosOne, 6(11) 2011



BMC Infect Dis. 2012 Nov 15;12:307. doi: 10.1186/1471-2334-12-307.

In vitro antimalarial susceptibility and molecular markers of drug resistance in Franceville, Gabon.

Zatra R, Lekana-douki JB, Lekoulou F, Bisvigou U, Ngoungou EB, Ndouo FS.

We conducted a cross-sectional study of 53 field isolates. Field isolates sensitivity to CQ, MF, DHA and MDAQ was assessed using the colorimetric DELI test.

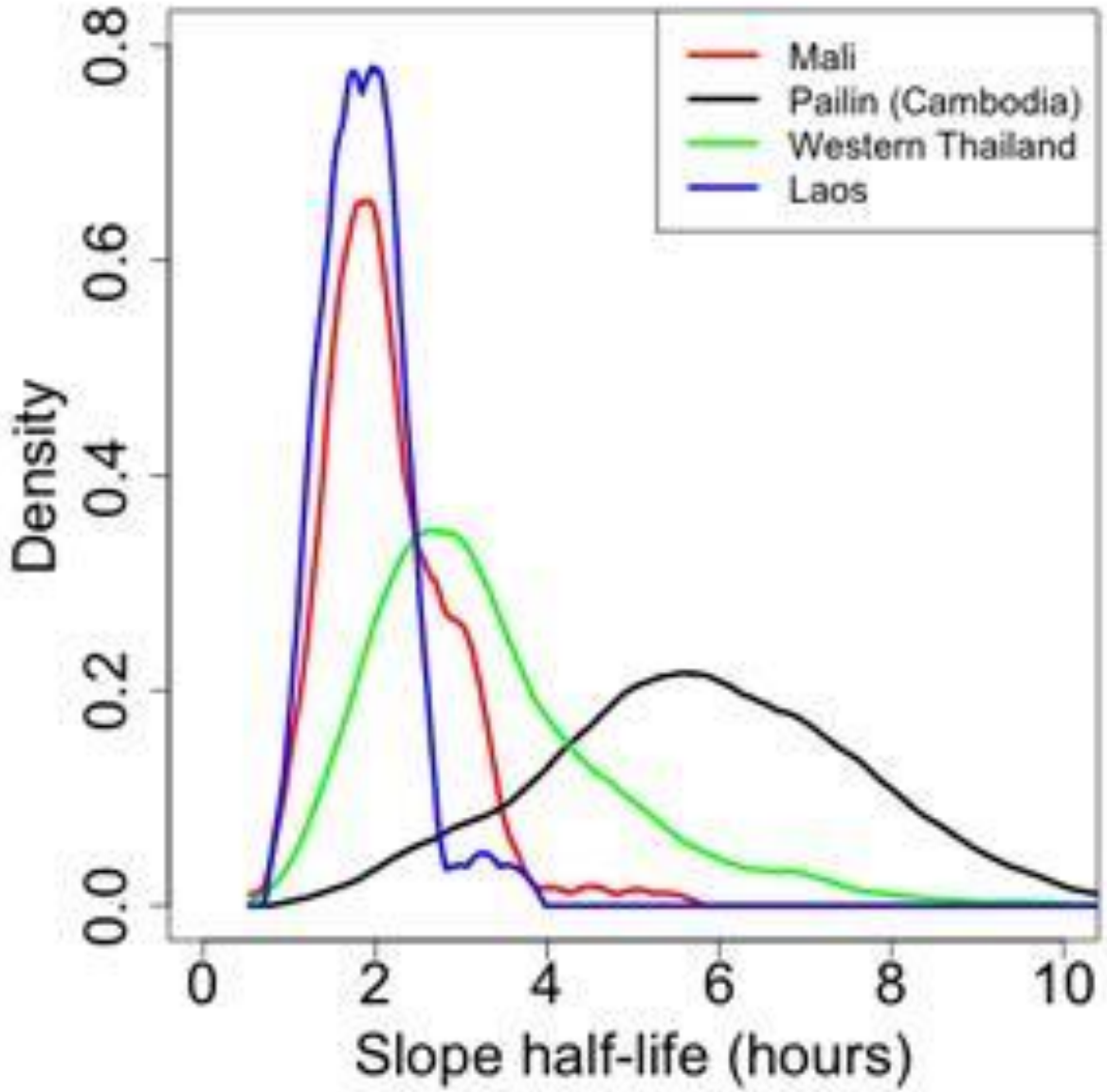
RESULTS:

The strongest correlation between diminished DHA sensitivity and MF resistance was observed (r2=0.73), followed by correlation between diminished DHA sensitivity and CQ resistance.

CONCLUSION:

These high levels of antimalarial drug resistance in Franceville, Gabon, call for reinforced surveillance of drug efficacy.

1.Jitan JK, Vreden SG, Adhin MR:
Emerging Coartem resistance assessed by day three parasitemia in Suriname.
2.Proceedings of the American Society of Tropical Medicine Meeting 2012, Atlanta, USA


Mali
Pailin (Cambodia)
Western Thailand
Laos
Density
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
Slope half-life (hours)

Mali

The Lancet Oct 22 2013

In a study conducted in Mbita, western Kenya, in 2009, Patrick Sawa, Teun Bousema and colleagues found that two major ACT regimens were both very effective at curing malaria among the 300 children who participated. But when they went further, and used a day seven blood sample from 77 and 80 children, respectively, from the two drug comparison groups for mosquito feeding, they found a significant difference between the two ACT formulations.

In Sudan

SP is recommended for iPTp and the availability of SP as an over-the-counter drug maintains the pressure on the parasite population. The efficacy of AS/SP is reaching the current threshold for anti-malarial policy change of 90%. Continuous use of SP as a partner to artesunate may be the cause of declined AS/P efficacy. In addition discontinuation of SP …is also recommended

NB Gadalla et al. Malaria J, 2013 12:255

We present the first evidence from an African efficacy study that amplification of the *pfmdr1* locus may contribute to recurrent *P. falciparum* parasitemia following Artemether-Lumefantrine therapy in Sudanese patients. This association needs to be confirmed in larger studies,

Gadalla NB et al., Antimicrob Agents Chemothera 2011, 55:5408-11

There was a statistically significant yearly increase of pfmdr1 N86 and pfcrt K76 between
2006–2011 from 14% to 61% and 14% to 35% after introduction of Coartem in Tanzania

An early warning sign

M Malmberg et al. Malaria Journal, 2013. 12-103

Trends in the prevalence of Artemether lumefantrine resistance associated alleles within Pfmdr1 and Pfcrt genes in Kenya

A Achleng

MIM Conference Durban 2013 Poster 008

Plasmodium falciparum with Multidrug Resistance Senegal

Aurélie Pascual,

This could be associated with rare clinical failures of *P. falciparum* infections to respond to mefloquine treatment or artemisinin-based combination therapy. However, our findings highlight the need for active surveillance and for ex vivo and in vivo studies in Senegal and in other parts of Africa

Emerg Inf Dis, May 2013, 19.

Sénégal, Thiès, Malaria Journal, 2013 12:441

Table 2 Parasite drug responses measured in the DAPI *ex vivo* assay

	2008 (N = 86)	2009 (N = 78)	2010 (N = 81)	2011 (N = 82)
Amodiaquine				
Median IC_{50}	9.6	6.5	11.2	14.5
IC_{50} Range	1.6, 1140	3.2, 36.7	1.0, 45.3	2.3, 53.7
90th percentile IC_{50}	24.0	11.8	22.2	35.4
Artemisinin				
Median IC_{50}	3.2	8.1	9.9	10.1
IC_{50} Range	1.1, 28.8	1.8, 36.7	1.9, 38.0	1.3, 73.1
90th percentile IC_{50}	9.3	17.0	22.4	24.9
Chloroquine				
Median IC_{50}	30.7	15.0	22.4	76.1
IC_{50} Range	1.4, 341.5	4.3, 205.5	8.1, 430.2	4.7, 455.0
90th percentile IC_{50}	199.4	108.2	199.1	364.6
Mefloquine				
Median IC_{50}	34.5	44.6	32.6	41.2
IC_{50} Range	1.6, 398.0	2.8, 92.1	9.2, 75.7	1.5, 191.5
90th percentile IC_{50}	84.6	62.5	59.0	82.4

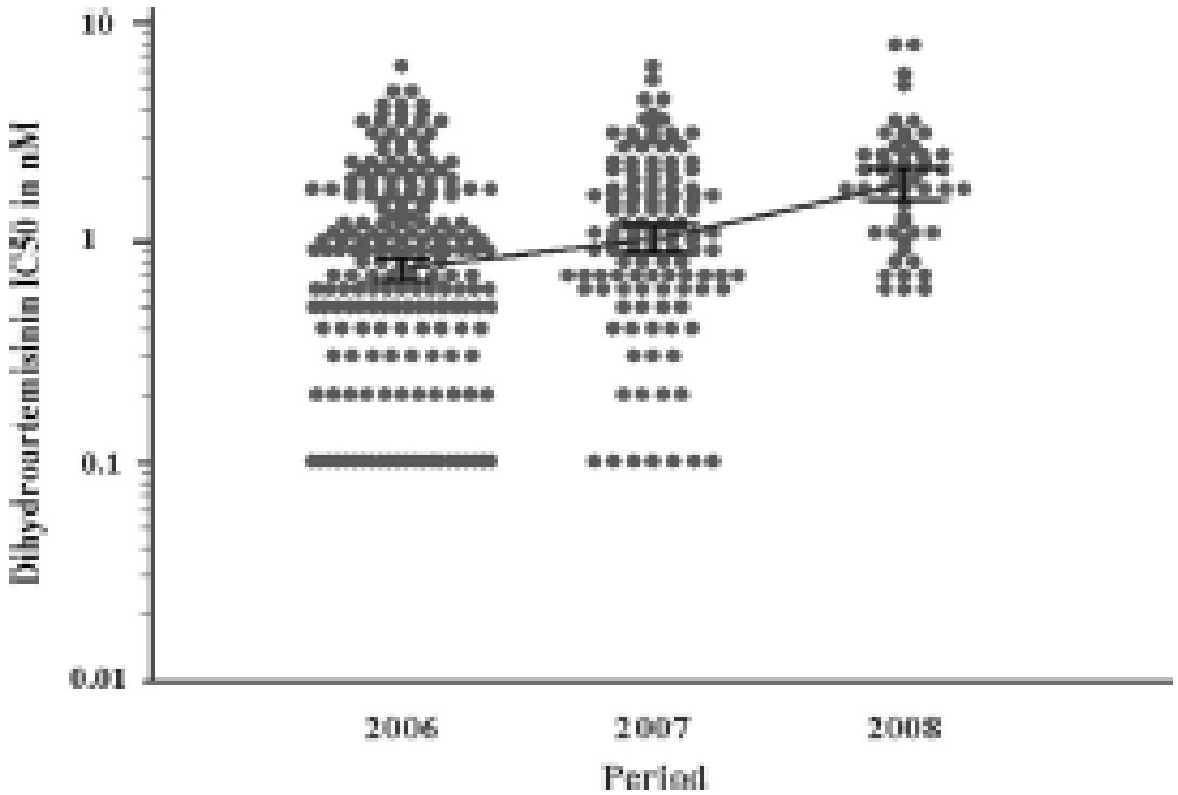


FIG. 4. Evolution of the DHA geometric mean IC_{50}s in *Plasmodium falciparum* isolates collected from 2006 to 2008 in patients with uncomplicated malaria at the sentinel sites of the antimalarial drug resistance surveillance network, Madagascar. The total numbers of isolates analyzed

Madagascar , Antimicrob Agents and Chemoth 2009 Aug

Possible artemisinin-based combination therapy-resistant malaria in Nigeria: a report of three cases

Rev Soc Bras Med Trop 46, 2013, 525-528

Uganda

H Bukirwa PloS Chemical trials 2006

Primary efficacy outcome was the 28-day risk of recurrent symptomatic malaria (AL = 27%;ASAQ = 42%) and recurrent parasitaemia (AL = 51%;ASAQ = 66%) both unadjusted for re-infection

Clinical Trial NCT00808951

Burkina Faso

… Artemether-Lumefantrine showing significantly higher occurence of recurrent infections during the 28-day follow-up period

A team of researchers from Canada and the United Kingdom studied parasites from travellers who returned to Canada with malaria after trips abroad between April 2008 and January 2011.

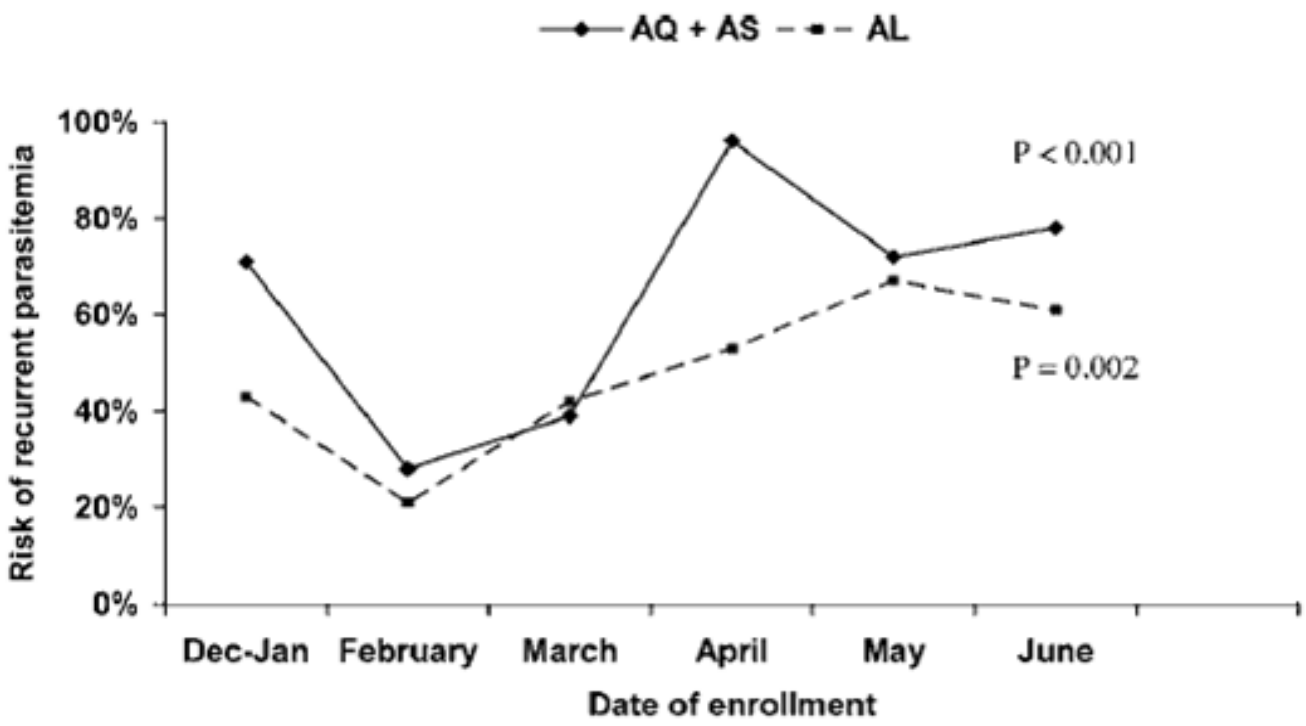
They found that 11 of the 28 parasites grown in the laboratory had a mutation that made them resistant to artemether, one of the artemisinin group of antimalarials.

All 11 came from Africa (from Angola, Cameroon, Congo, Ghana, Kenya, Liberia, Nigeria and Tanzania), the researchers reported
last month (27 April) in Malaria Journal.

The high potential for resistance is known since 5 years !

Recurrence rate for ACTs in Uganda, H.Bukirwa et al., PlosClinicalTrials, May 2006

AQ+AS: amodiaquine + artesunate
AL: artemether+lumefantrine



Or 7 years

TK Mutabingwa et al
Lancet, 365 , 2005, 1774-80.

By day 28 the parasitological failures were 40 % for artesunate –amodiaquine and 21% for artemether-lumefantrine on Tanzanian children

Lancet. 2005 Dec 3;366(9501):1960-3.

Resistance of Plasmodium falciparum field isolates to in-vitro artemether and point mutations of the SERCA-type PfATPase6.

Jambou R, L

Or 10 years ago

In M'lomp, Senegal, even though a decline in the incidence rate of uncomplicated malaria was observed between 1998 and 2002, it was slight and the impact of ACT (ASAQ) introduction could not be clearly established.

S Sarrasat et al., Malaria Journal 7, 2008, 215

Or 10 years ago in Cambodia

In 2001-2002 in Sampouv Loun, resistance to artemether-lumefantrine was already alarmingly high at 28% and this drug was replaced by artesunate-mefloquine which had to be discontinued too because of failures

WHO report ISBN 9789241501644

Or 12 years ago

C.Wongrichanalai et al.,
Bulletin of the World Health Organisation, 1999, 77 (5)

Our results suggest that that combination with mefloquine is not the ideal way of protecting the usefulness of artemisinin and its derivates

18 years ago

Il existe un risque important de résistances croisées entre l‘artemether et la méfloquine ou l‘halofantrine. Il convient d‘être vigilant…

P. Ringwald et al., Bull liais.doc-OCEAC 27, 1994, 27-29

Or even 25 years

Qinghaosu (artemisinin derivatives) resistance in rodent malaria

A.N. Chawira,
•D.C. Warhurst,
•W. Peters
Dept. of Medical Protozoology, London School of Hygiene and Tropical Medicine, London, WC1E 7HT U.K.

Accepted 25 October **1985**.

*Artemisia annua n'*a jamais donné le moindre signe de résistance au cours de 2000 années d'utilisation, ni dans les essais cliniques que nous avons faits au

Coût du traitement/patient/année

° HIV/AIDS: 800 €

° TB: 100 €

° Malaria (A annua): 1 €*

° Dysentery(A annua): 0.5 €

Avec 1000€ on peut sauver la vie de 1000 enfants

- En évitant les crises palu sévère
- En stimulant l’immunité pour éviter les rechutes

Pas nécessairement en éliminant du sang tous les parasites comme les ACT prétendent le faire