

Update on artesunate/mefloquine study in Suriname

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Background

- ▶ In a study carried out in 2011 a sharp increase of day 3 parasitaemia was detected in patients treated with Coartem (compared to 2006)
 - (Mem. Inst. Osw. Cruz Dec. 2013)

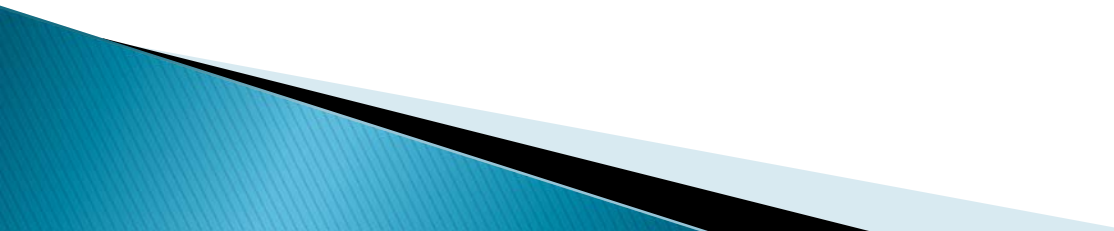
Day 2 and 3 parasitaemia after Coartem in 2011

Table II: Parasitological assessment day 0, 2, 3			
	2005/2006	2011	
Day 0 parasitaemia ^a			
Geometric mean	9 588.98	2 757.88	^b <i>p</i> < 0.001
Range	512 – 82 057	215 - 89 880	
Median	12 541.00	2 445.00	
25 th Percentile	4 616.00	682.75	
50 th Percentile	12 541.00	2 445.00	
75 th Percentile	24 879.50	8 524.00	
Inter quartile range	20 263.5	7 841.25	
Percentage of patients with parasitaemia on day 2 and 3			
PPP48	18 % (8/44) ^c	75 % (36/48)	^d <i>p</i> < 0.001
PPP72	2 % (1/45)	31 % (15/48)	^d <i>p</i> < 0.001
^a Asexual parasites/mm ³			
^b Mann-Whitney U test			
^c Data from one patient in 2005/2006 on day 2 was missing and was therefore excluded when determining the PPP48			
^d Fisher's Exact test			
PPP48; Percentage of patients with parasitaemia on day 2 (48 hours), PPR72; Percentage of patients with parasitaemia on day 3 (72 hours).			

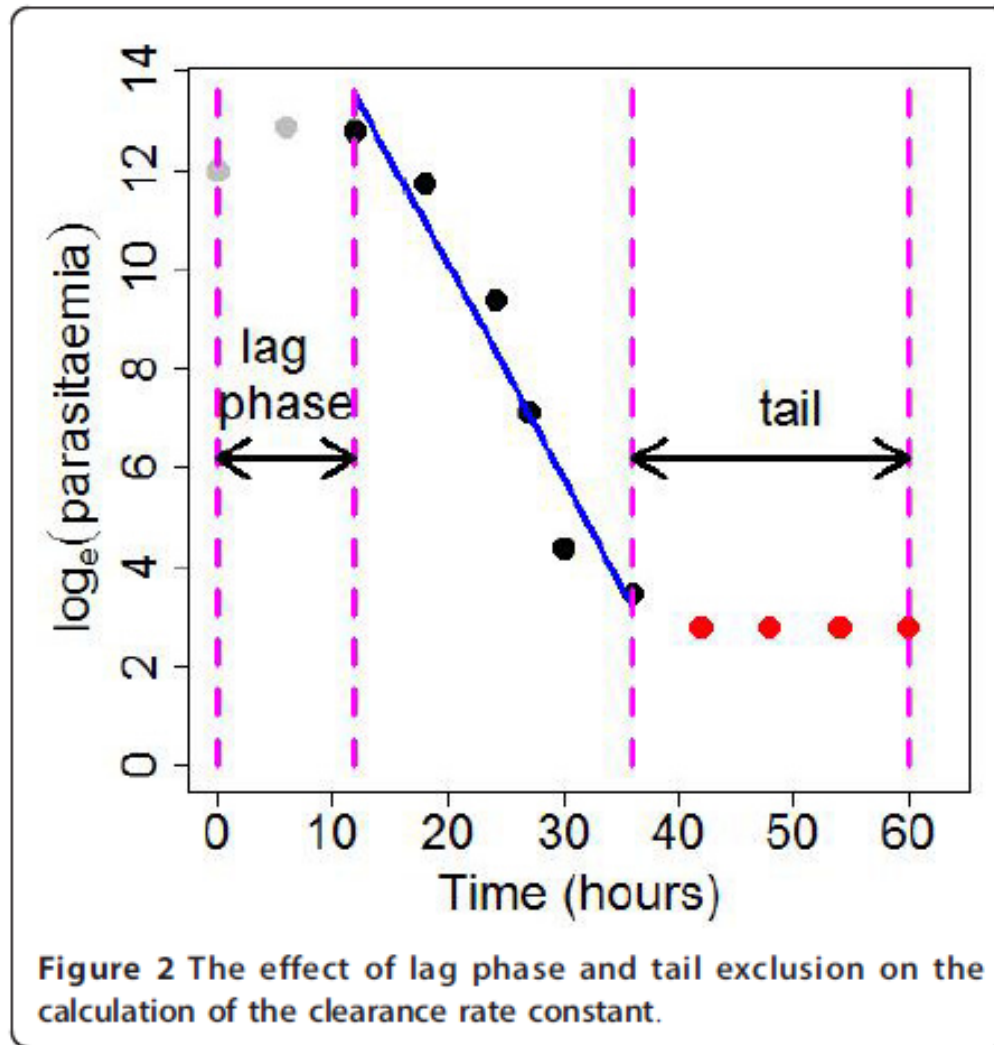
Treatment efficacy Coartem 2011

- ▶ All eleven participants followed until day 28 had ACPR

Background (2)

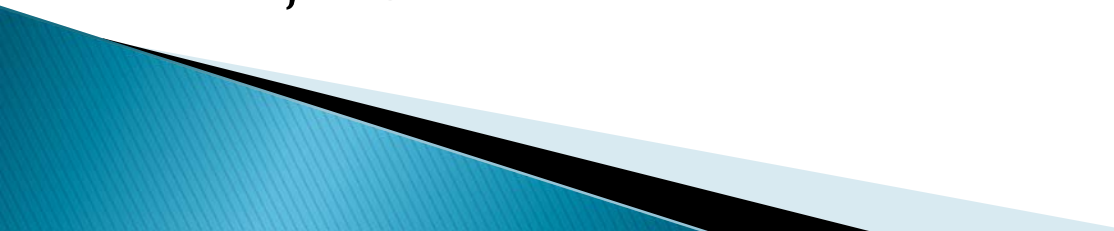
- ▶ It was concluded that this could be an indication of decreasing sensitivity to artemisinin.
 - ▶ However, day 3 parasitaemia (using an ACT) is considered to be a too inaccurate tool to confirm this.
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Parasite Clearance Rate

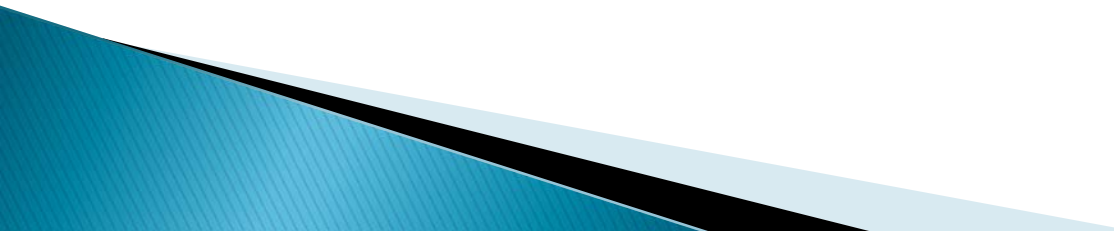


Flegg et al. Standardizing the measurement of parasite clearance in falciparum malaria: the parasite clearance estimator. *Malaria Journal* 2011, 10:339

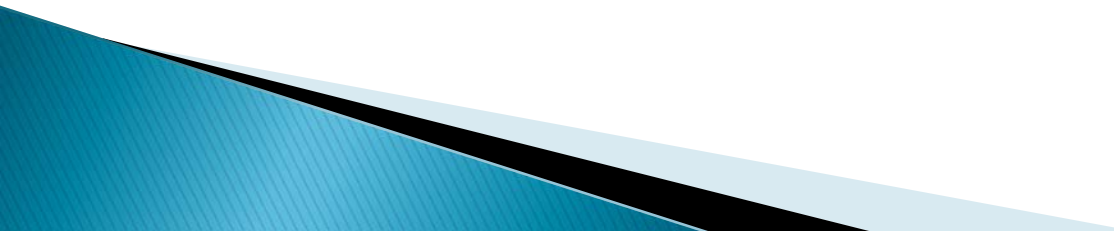
Study protocol parasite clearance rate using artesunate for 3 days

- *P. Falciparum* mono-infection, 200 – 10.000 par/ul
 - Artesunate OD 4 mg/Kg/day for 3 days DOT
 - After 72 h mefloquine and primaquine
 - Thick smears every 8 h until 80 h
 - If possible, continue follow up on Day 7, 14, 21, 28
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Specific measures to improve follow up and slide preservation

- Participants are offered to stay in a hotel during the first 3 days to allow better follow up.
 - Participants are offered compensation for lost working time in the gold mines.
 - Slides are better preserved (covered), to allow quality control at any time.
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Preliminary results

- ▶ Study started on July 8 2013
 - ▶ So far, 35 patients enrolled (March 05 2014)
 - ▶ Rate of enrollment decreasing since September.
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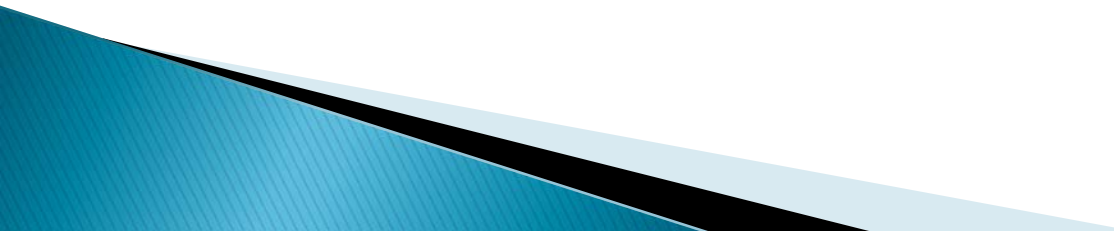
Characteristics of enrolled subjects: Origin

- ▶ Fr. Guyana: 29 patients
 - Eau Claire 11,
 - Sophie 11,
 - Pedi Limao 3,
 - Cacao 2,
 - Marrodeira 2
- ▶ Guyana: 2 patients (Elash)
- ▶ Suriname: 2 patients (Benzdorp)
- ▶ Unknown: 2 patients

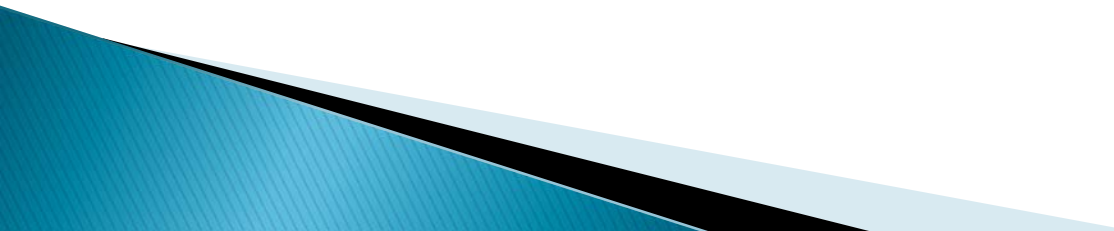
Characteristics of enrolled patients: age/sex

- ▶ All adults (>18 years)
- ▶ Males: 18 females: 17

Follow up

- ▶ Exclusions: 4 (2 artecom use, 2 refusals)
 - ▶ Follow up beyond day 3: 31
 - ▶ Follow up until day 28: 7 (All ACPR)
 - ▶ Still being followed: 1 (beyond day 3)
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Day 3 parasitaemia

- ▶ All Patients, except 3 (10 %) , had negative slides at 72 hours after the first dose of treatment.
 - ▶ The incidence of parasite clearance at day 3 was much higher than expected!
 - ▶ The data however, need still to be entered in the clearance estimator.
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Better efficacy of artesunate compared to artemether?

Current results, though preliminary, may point into this direction.

Literature?

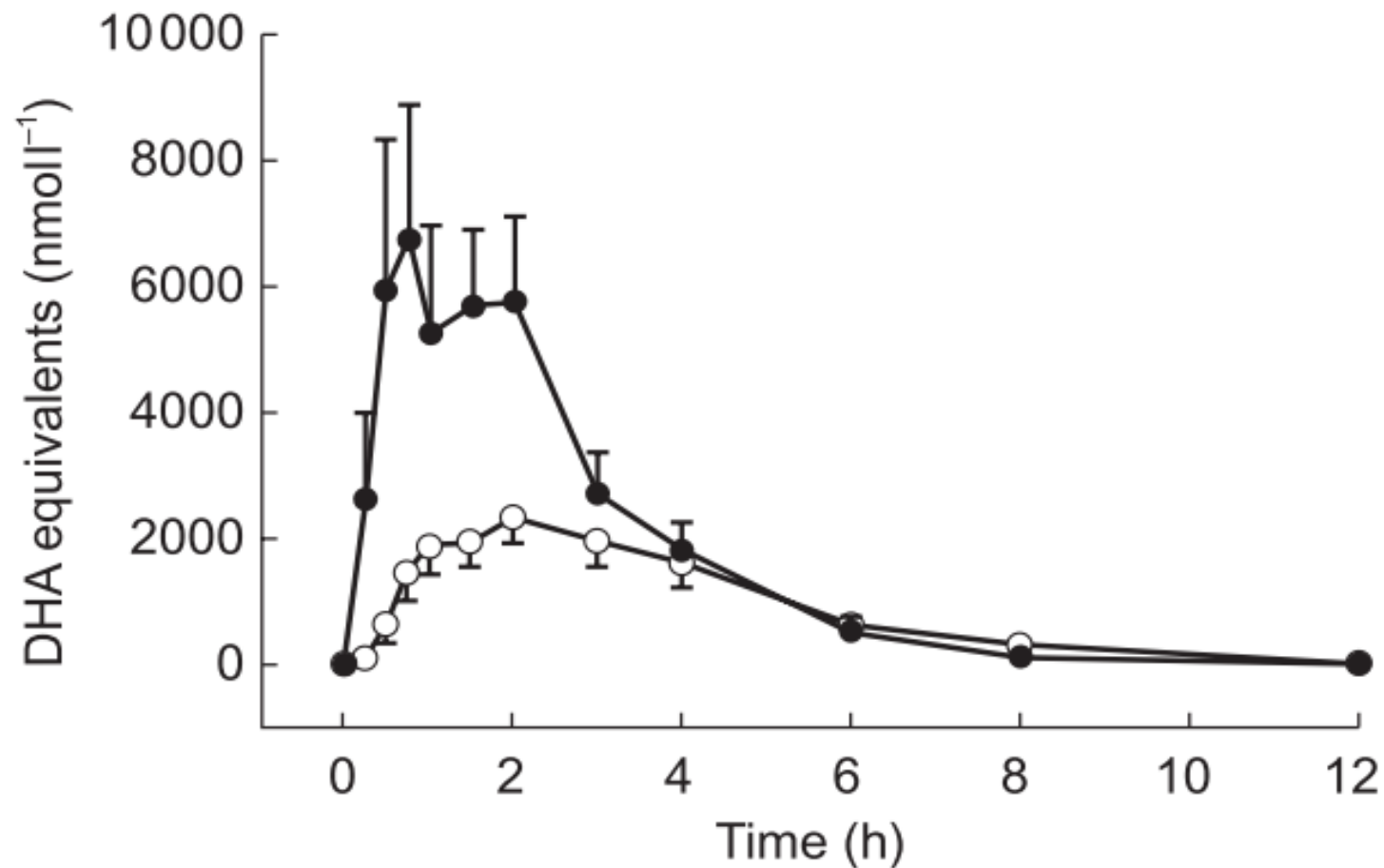


Figure 1 Mean antimalarial activity (\pm s.e. mean) in DHA equivalents for oral administration of artesunate (●) and artemether (○) during the first 12 h after drug administration. Days 1 and 2 combined.

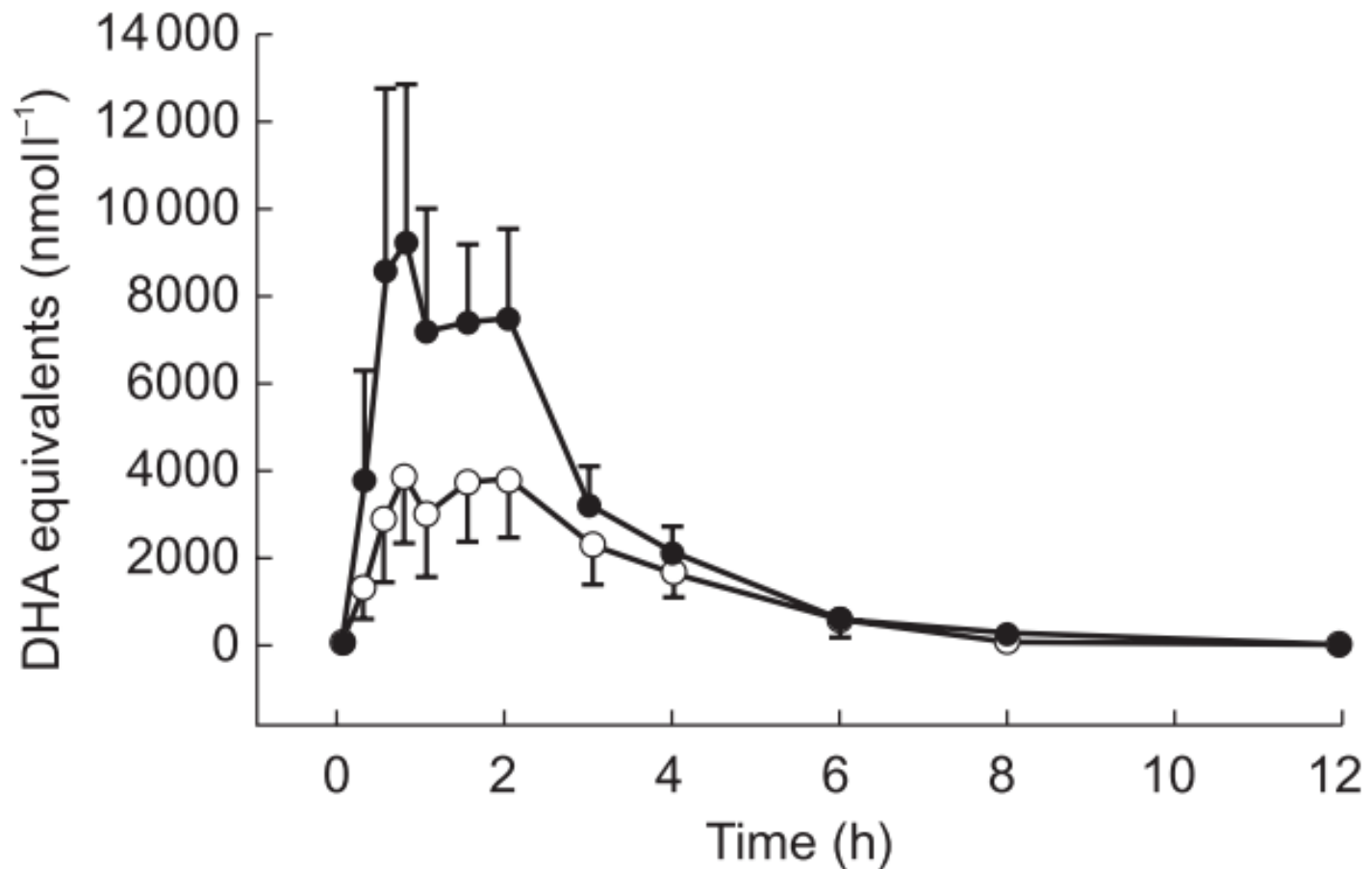


Figure 2 Mean antimalarial activity (\pm s.e. mean) in DHA equivalents for oral administration of artesunate, on the first (○) and second day (●), during the first 12 h after drug administration.

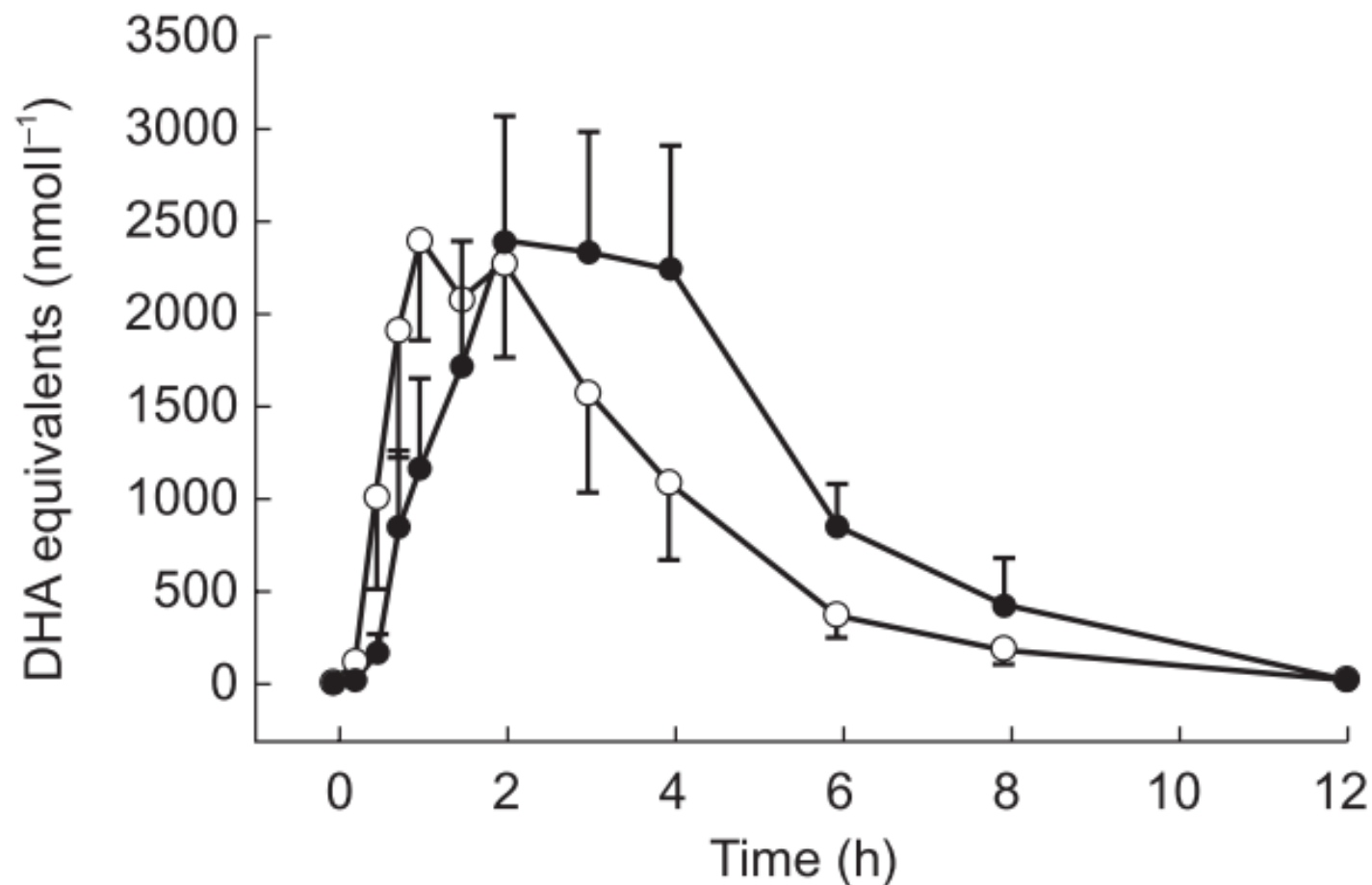


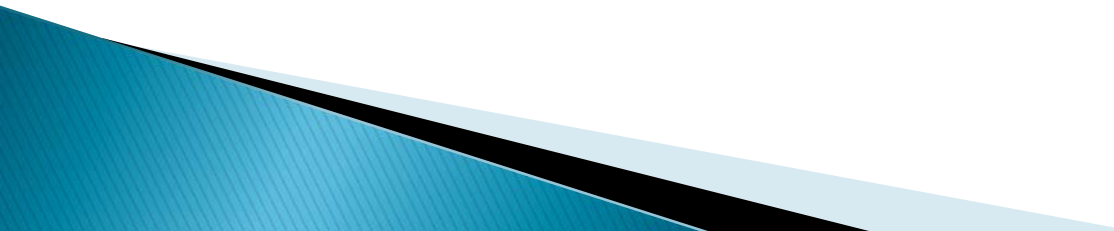
Figure 3 Mean antimalarial activity (\pm s.e. mean) in DHA equivalents for oral administration of artemether, on the first (○) and second day (●), during the first 12 h after drug administration.

**But in vivo parasite
clearance was similar for
both drugs!!**

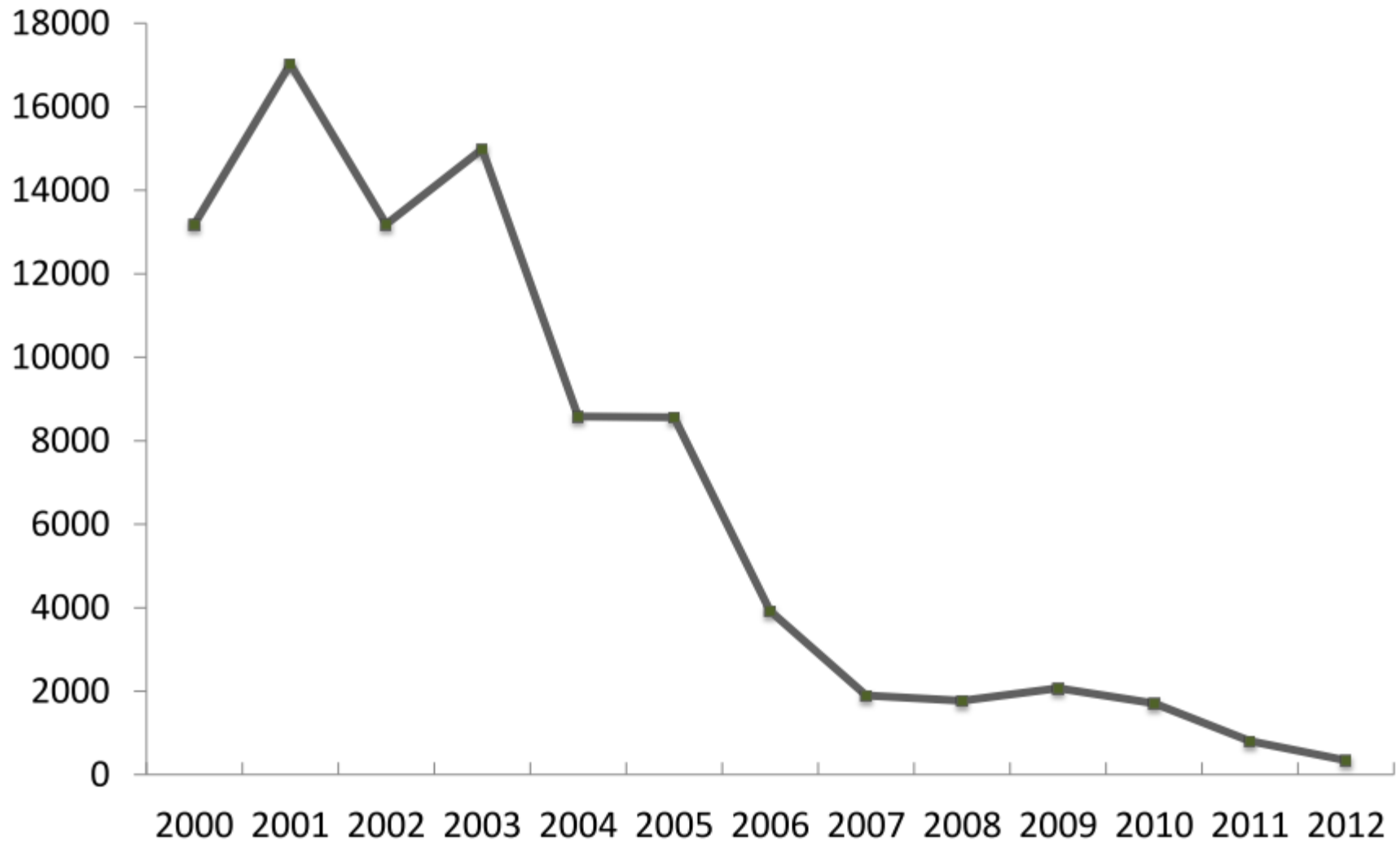


“Despite a 29% lower molar dose, oral artesunate had a significantly higher antimalarial activity than oral artemether ($p < 0.02$)”.

Possible future exercises

- Compare oral artemether to artesunate 3 days?
 - Compare Coartem to artesunate 3 days?
 - Assess parasitaemia at 48 h?
 - Compare efficacy of different artemisinins *in vitro*?
 - Similar studies possibly no longer feasible in Suriname!
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Malaria cases Suriname 2000-2012



Suriname Bureau of Public Health nov 2012

Hiwat et al. Novel strategies lead to pre-elimination of malaria in previously high-risk areas in Suriname, South America Malaria Journal 2012, 11:10

Possible future measures

- Multiple first line ACT treatments?
- Switch to artesunate/mefloquine as a first line?
- Increase the dose of artemether in Coartem?
-?

Muito Obrigado

Merci Bien

Thank You

Muchas Gracias

Dank u wel