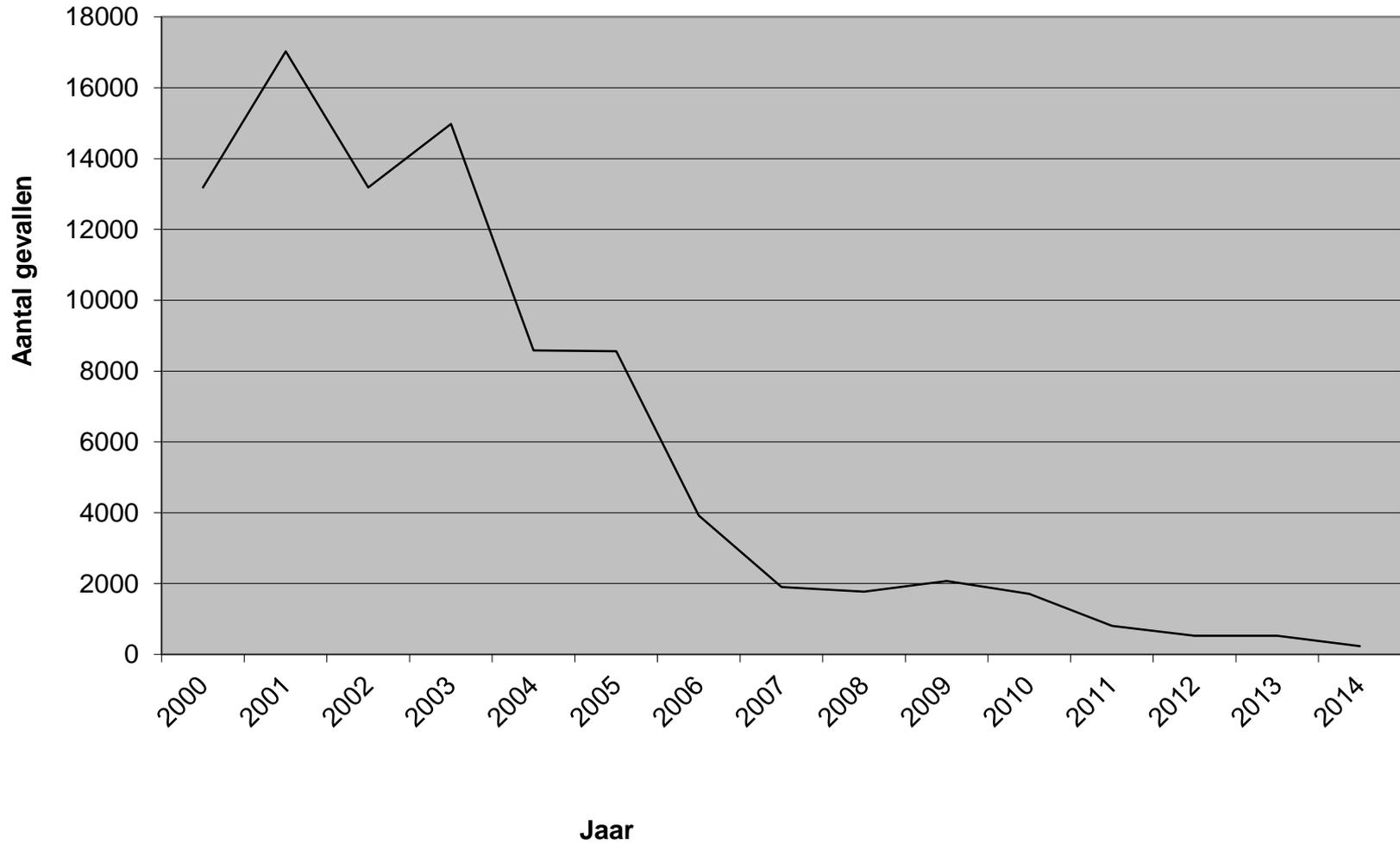


Assessment of artemisinin resistance of *Plasmodium falciparum* malaria in Suriname

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Bevestigde malariagevallen 2000- november 2014



Malaria in Suriname

- Numbers are continuously decreasing
 - (2015 so far only 6 locally transmitted cases (4 *P.v.*, 2 *P.f.*)
- Threat of resurgence due to decreasing sensitivity?
- Assessing efficacy by traditional efficacy studies currently virtually impossible

Challenges for efficacy studies in Suriname

- Low number of cases, virtually only gold miners
- Population of gold miners is not available for 28 days follow up
- Assessing day 3 parasitaemia, difficult but feasible

Working definition of artemisinin resistance

- Discussed during the GPARC process and at the Fogarty Internal Center and NIH meeting in November 2010
- WHO is using working definition as below:
 - an increase in parasite clearance time, as evidenced by greater than 10% of cases with parasites detectable on day 3 following treatment with an ACT (suspected resistance); or
 - a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence after day 7 of parasites within 28/42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration (confirmed resistance).

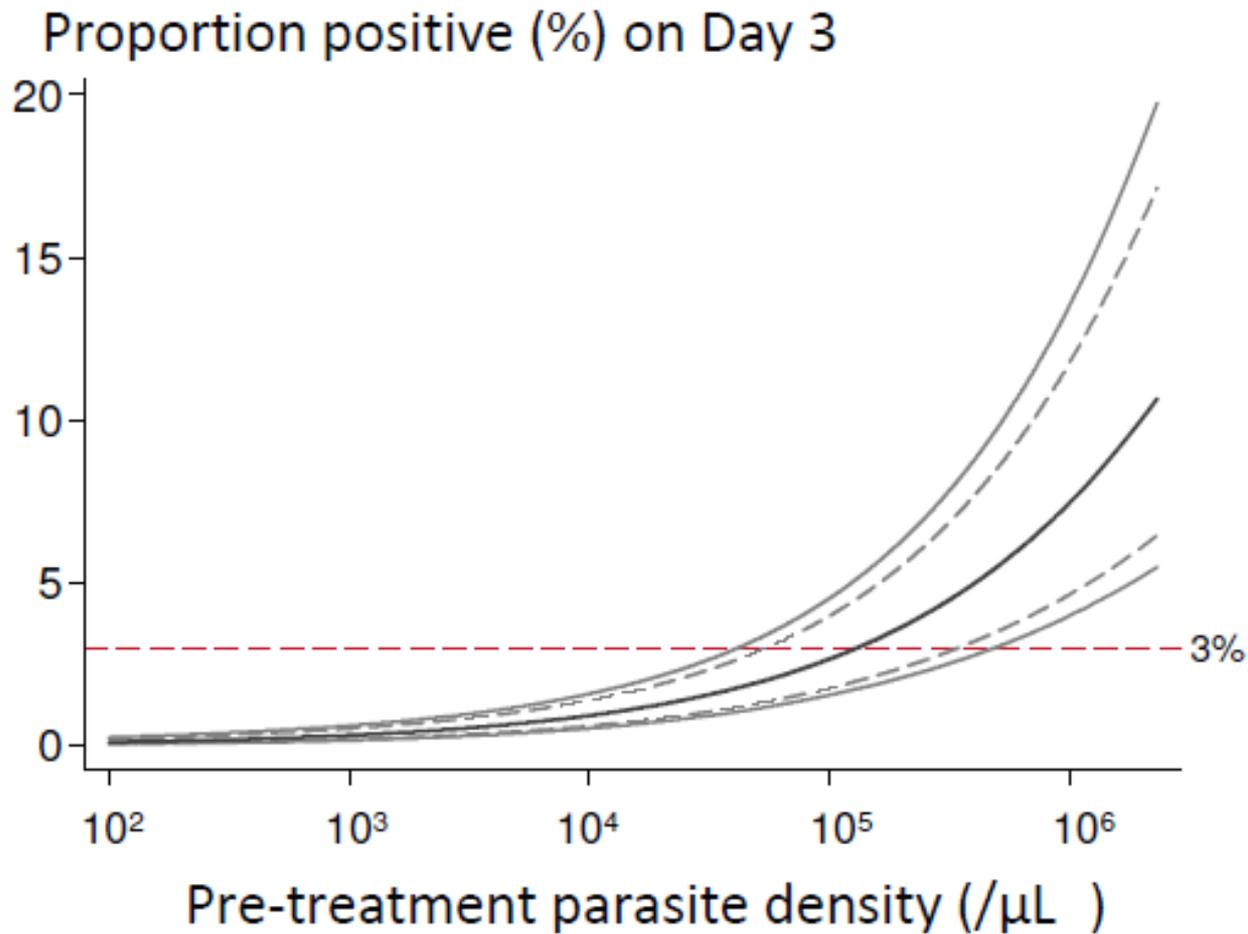


Figure 7 The proportion of patients with fully artemisinin sensitive *P. falciparum* infections who are slide positive on day 3 are shown with 95 and 99% confidence intervals. From Stepniewska et al with permission [45].

Assessment of Day 3 Parasitaemia in patients treated with Coartem

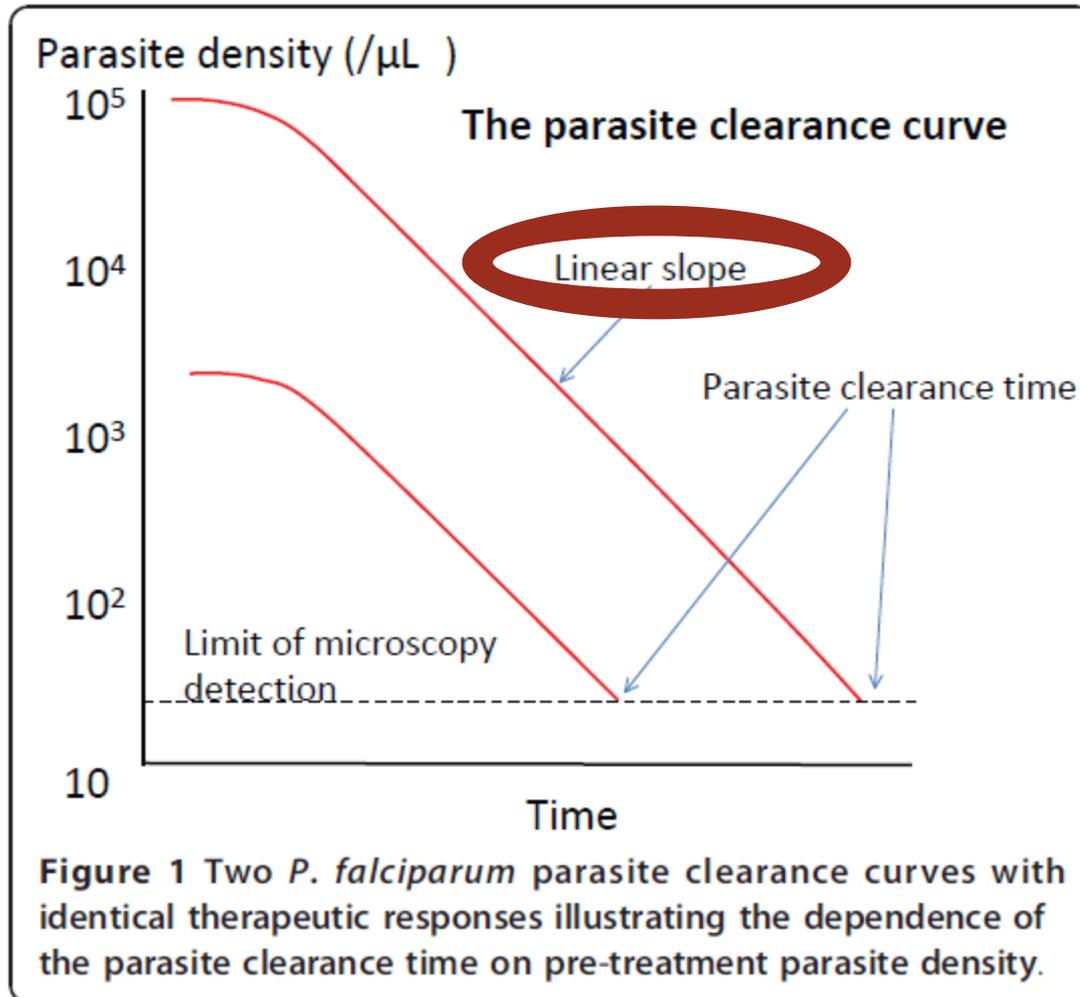
	2005/2006 (n = 45)	2011 (n = 48)	
Day 2 Parasitaemia			
Number of positive cases (percentage)	9 (20 %)	36 (75 %)	^a p < 0.001
Day 3 Parasitaemia			
Number of positive cases (percentage)	1 (2.2 %)	15 (31.3 %)	^a p < 0.001
^a Fisher's Exact test			

Note: All patients followed until day 28 had cleared their parasites.

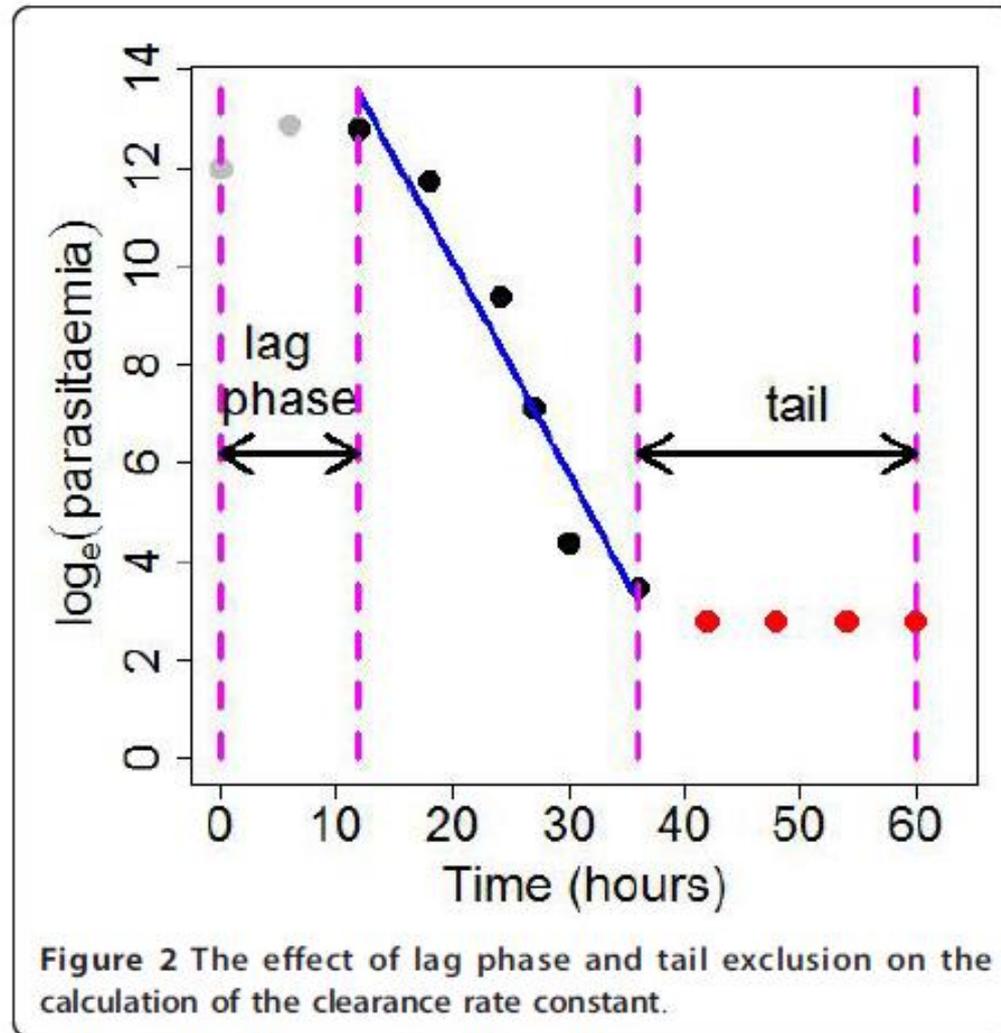
Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. 108(8): 986-973, December 2013.

Parasite clearance rate

- Parasite clearance rate: $d(\text{parasite density})/d(t) = C$; linear association



Parasite Clearance Estimator (PCE)



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

WHO definition for resistance to artemisinin assessed by P.C.E.

More than 10 % of patients with a parasite clearance half-life of > 5 h.

Protocol for Parasite clearance study 2013/14

- Our study in 2011 was conducted with Coartem (artemether/lumefantrine)
- Artemether is not available as a single agent.
- Therefore we used artesunate

Protocol for Parasite clearance study 2013/14

- **Patients with *P. falciparum* mono-infection.**
- **Parasitaemia: 200 - 10 000/ μ l**
- **Artesunate 4 mg/Kg OD for 3 days, followed by mefloquine and primaquine after day 3.**
- **Assessment of parasitaemia every 8 h until clearance of parasites, thereafter on day 7, 14, 21, 28 (if still available for the study).**

Results study 2013/14

- **45 Patients enrolled**
- **38 Patients evaluable**
- **Withdrawn: 7 patients (wrong inclusion, protocol violation, refusal to continue)**

Characteristics of enrolled subjects:

Origin

- Fr. Guyana: 36 patients
 - Eau Claire 14,
 - Sophie 15,
 - Pedi Limao 3,
 - Cacao 2,
 - Marrodeira 2.
- Guyana: 4 patients (3 Elash, 1 Aramu)
- Suriname: 3 patients (Benzdorp)
- Unknown: 2 patients

Characteristics of enrolled patients: age/sex

- All adults (>18 years)
- Males: 25 females: 20

Follow up

- Follow up beyond day 3: 38
- Follow up until day 28: 8 (All ACPR)

Results (c'td)

- **22 Patients parasitaemic on day 2 (57.9 %)**
- **3 Patients parasitaemic on day 3 (7.9 %)**

- **All patients followed until day 28 had cleared the parasite**

- **Mean initial parasitaemia: 9.635,62 par./ μ L**
- **(In study of 2011: 10.003.92 par./ μ L**

Parasitaemia half-life using WWARN parasite clearance estimator

- 20 patients ≤ 5.5 h
- 19 patients > 5.5 h (48.7 %)
- 7 patients > 7 h (17.9 %)
- 2 patients > 10 h

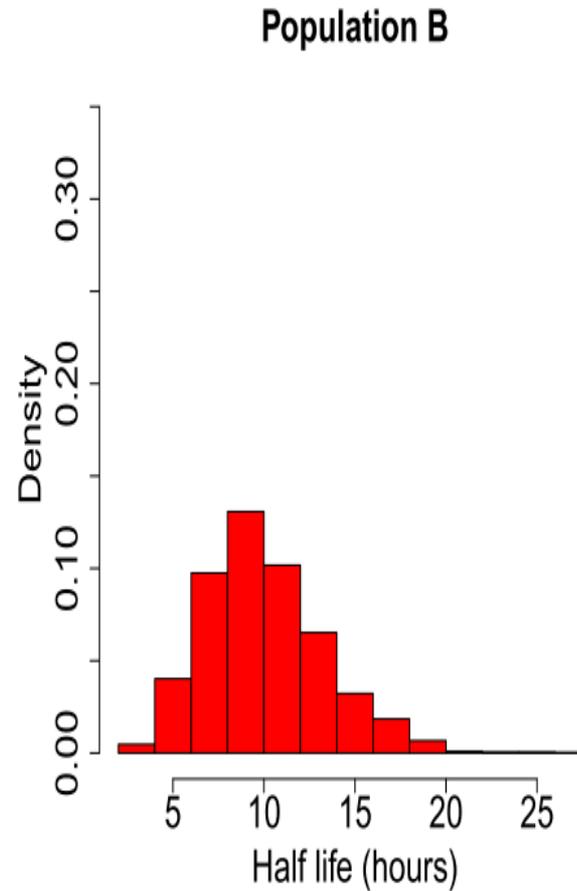
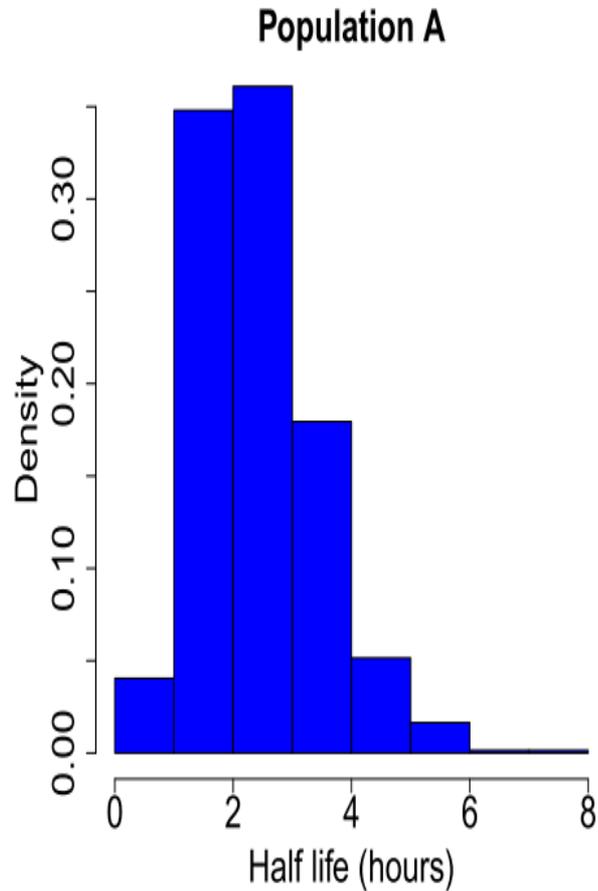


Figure 1: Stylised graphs showing the distribution of parasite clearance half lives for two populations: population B shows evidence of prolonged clearance, when compared to population A.

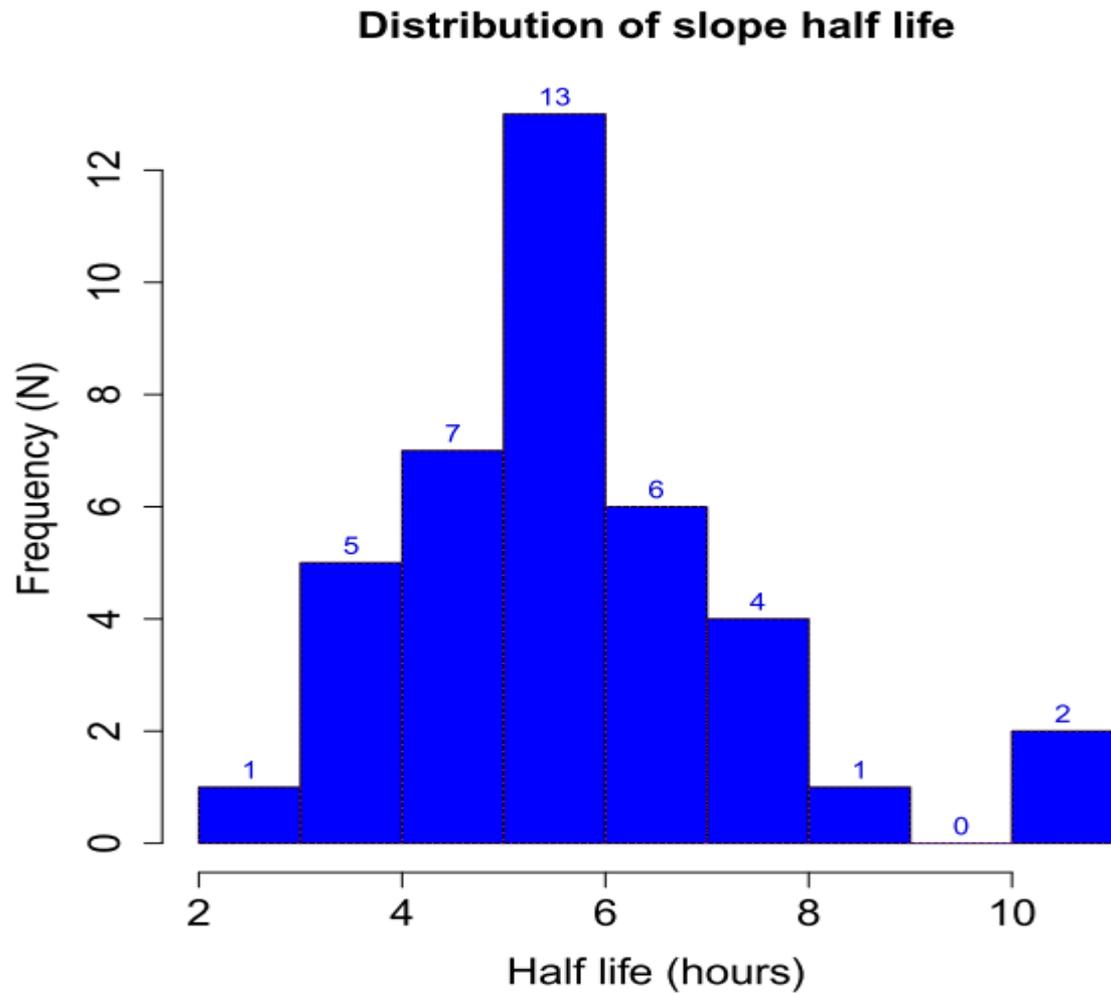


Figure 4: Distribution of slope half life

Conclusions artesunate study:

- **Day 3 parasitaemia 7.9 %**
 - (Coartem study in 2005 2% and in 2011: 31%)
- **Day 2 parasitaemia 57.9%**
 - (Coartem study in 2005: 20% and in 2011: 75%)
- **>5 h parasite clearance half-life : 48.7%**
 - (WHO threshold 10 %)

ARTICLE

doi:10.1038/nature12876

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

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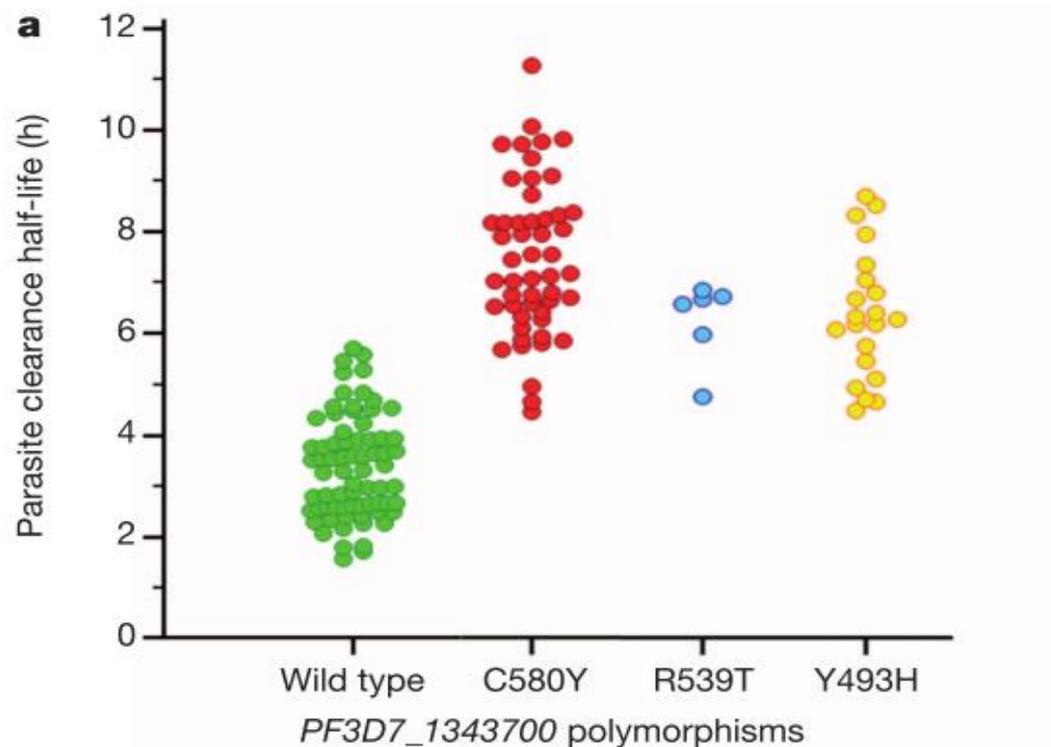


Figure 4 | Parasite clearance half-lives. **a**, Correlation of parasite clearance half-lives and K13-propeller alleles for parasite isolates in Pursat and Ratanakiri in 2009–2010. Wild-type parasites have shorter half-lives (median 3.30 h, IQR 2.59–3.95, $n = 72$) than C580Y (7.19 h, 6.47–8.31, $n = 51$, $P < 10^{-6}$, Mann–Whitney U test), R539T (6.64 h, 6.00–6.72, $n = 6$, $P < 10^{-6}$) or Y493H (6.28 h, 5.37–7.14, $n = 21$, $P < 10^{-6}$) parasites. The half-life of C580Y parasites is significantly longer than that of Y493H parasites ($P = 0.007$). **b**, Correlation of

Assessment of 'K13' mutations in isolates from the 2013/14 study in Suriname

- Carried out by CDC, Atlanta
- In none of the isolates the K13 mutation has been detected.

Summary

Artesunate mefloquine study 2013/'14

- **This combination therapy is still highly efficacious in the treatment of *P. falciparum* malaria in our region.**
- **Day 3 parasitaemia rate is lower than 10 %.**
- **The 48.7 % rate of parasite half life > 5.5 h suggests a reduced sensitivity to artesunate.**
- **K13 mutation was not found in our samples.**
- **Molecular studies looking for other mutations are underway.**

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Study collaborators and volunteers

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- **Mr. Jeetendra K. Jitan, Bsc, Ministry of Health, Suriname**
- **Dr. Pascal Ringwald, WHO, Geneva**
- **Lab technicians, fieldworkers, administrative staff**
- **The patients, who volunteered to participate**

Thank You!