Dev Care foundation

MRG

What is new in Malaria?

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BSM 21-22 March 2015

Outline

- **Clinical aspects**
- **Treatment guidelines**
- **Artemisinin resistance**

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Severe Malaria

World Health Organization

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WILEY Blackwell

Swiss TPH

Outline bedside clinical classification of severe malaria in children in a high-transmission area

Group 1.	**Children at increased risk of dying immediately who require parenteral antimalarials and supportive therapy**
	a) Prostrated children (prostration is the inability to sit upright in a child normally able to do so, or to drink in the case of children too young to sit). Three subgroups of increasing severity should be distinguished.
	(i) Prostrate but fully conscious
	(ii) Prostrate with impaired consciousness but not in deep coma
	(iii) Coma (the inability to localise a painful stimulus)
	b) Respiratory distress (acidotic breathing)
	(i) Mild - sustained nasal flaring and/or mild intercostal indrawing (recession)
	(ii) Severe - the presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing
	c) Shock

Outline bedside clinical classification of severe malaria in children in a high-transmission area contd.....

Group 2.	**Children who, though able to be treated with oral antimalarials, require supervised management because of the risk of clinical deterioration but who show none of the features of group 1 (above)*.**
	a) Children with a haemoglobin <5g/dl or haematocrit < 15% **b) Children with 2 or more convulsions within a 24-hour period** **c) Haemoglobinuria (blackwater)**
Group 3.	**Children who require parenteral treatment because of persistent vomiting but who lack any specific clinical or laboratory features of groups 1 or 2 (above).**

Outline bedside clinical classification of severe malaria in adults

Group: 1

- **Adults at increased risk of dying immediately who require parenteral antimalarials and appropriate supportive therapy**
- **Prostrated or obtunded adults (prostration is the inability to sit or to drink). Three subgroups of increasing severity should be distinguished**
  - **Prostrate but fully conscious.**
  - **Prostrate with impaired consciousness but not in deep coma (GCS $\geq$ 11)**
  - **Confusion and agitation (GCS $\geq$ 11)**
  - **Coma (the inability to localise a painful stimulus) (GCS < 11)**
- **Respiratory distress (acidotic breathing)**
  - **Mild - sustained nasal flaring and/or mild intercostal indrawing (recession).**
  - **Severe - the presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing.**
- **Shock**
- **Anuric patients**
- **Significant upper gastrointestinal haemorrhage**

Outline bedside clinical classification of severe malaria in adults contd...

Group: 2

- **Adults who, though able to be treated with oral antimalarials, require supervised management because of the risk of clinical deterioration but who show none of the features of group 1 (above).**
- **Adults with a haemoglobin <7g/dl or haematocrit < 20%;**
- **Adults with 1 or more convulsions within a 24-hour period.**
- **Haemoglobinuria (blackwater)**
- **Jaundiced patients**

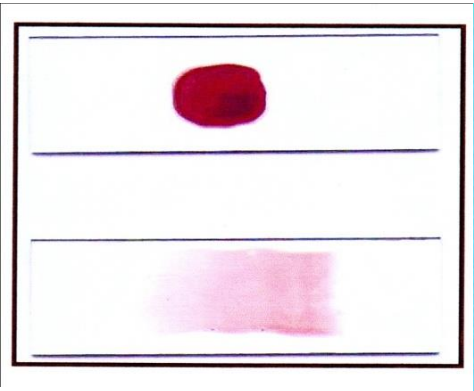
Group: 3

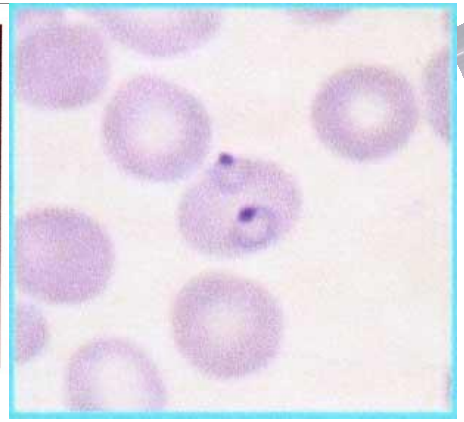
- **Adults who require parenteral treatment because of persistent vomiting but who lack any specific clinical or laboratory features of groups 1 or 2 (above).**
- **If parasite counts are immediately available a parasitaemia over 4% should be included in group 2.**

Diagnosis of Malaria

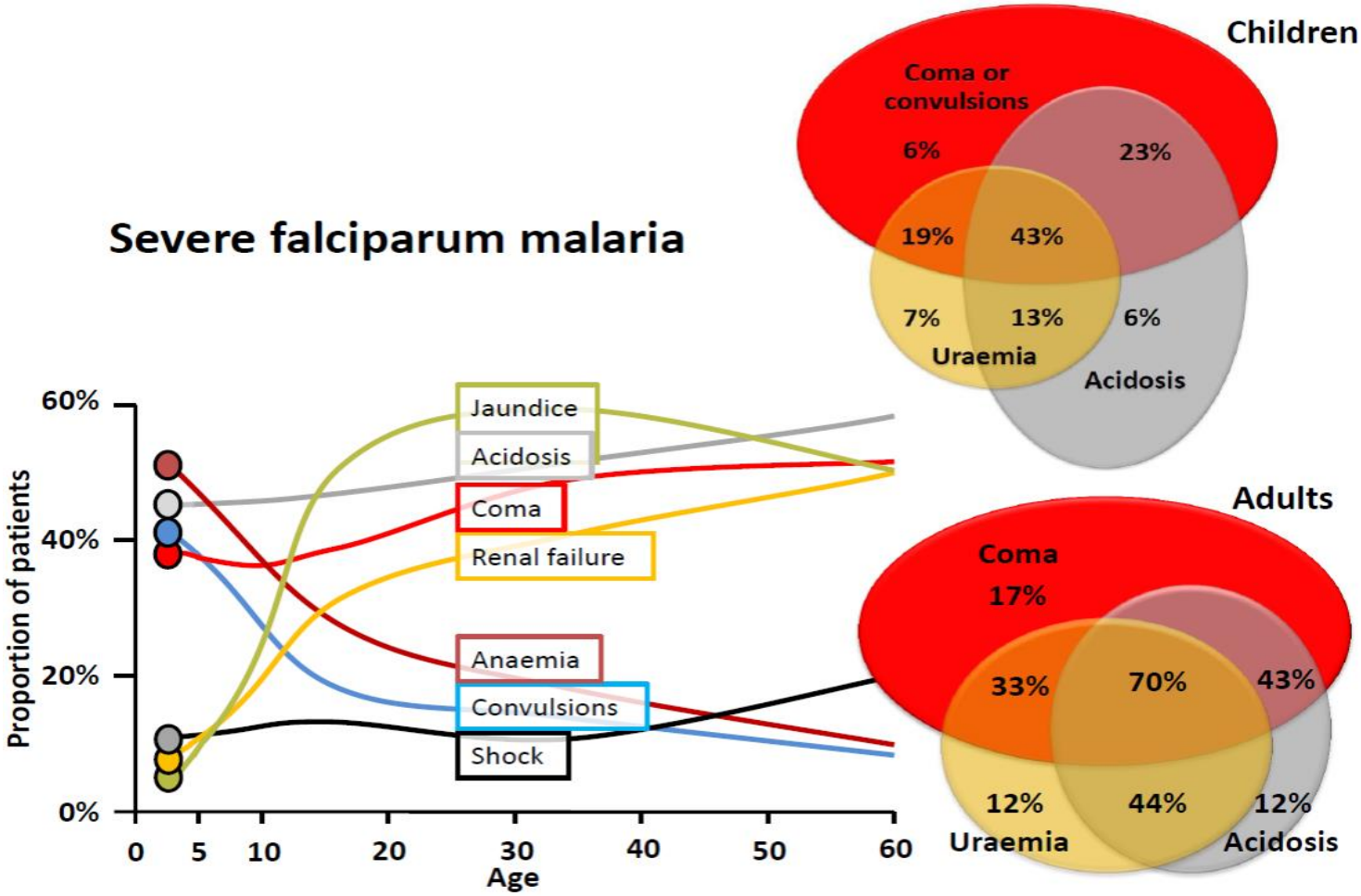
- **All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.**
- **Use of both microscopy and RDTs should be supported by a quality assurance programme.**

(Good practice statement)

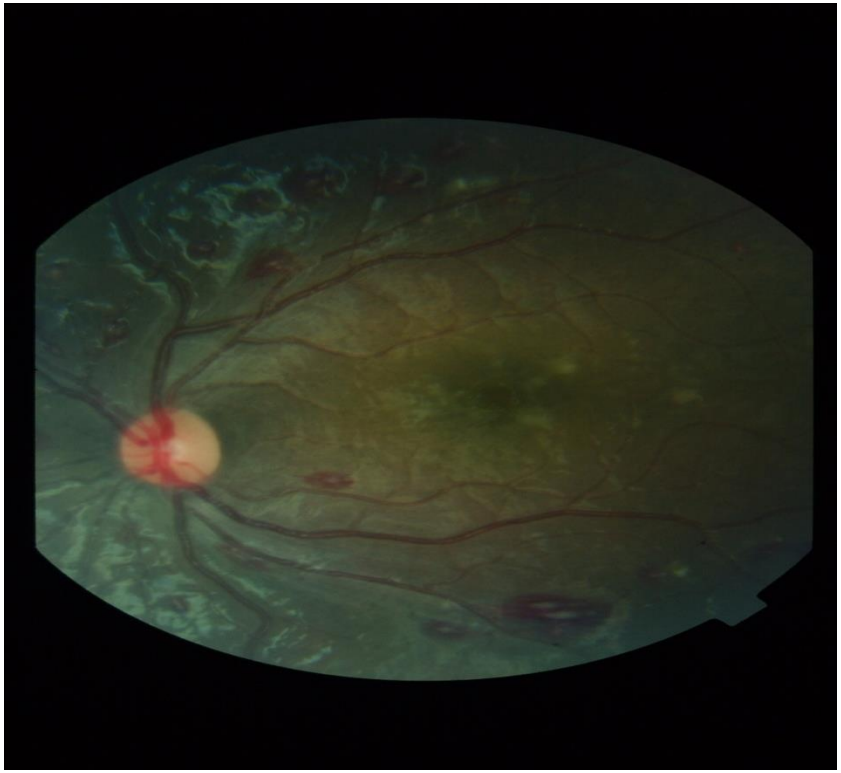




Severe Falciparum Malaria



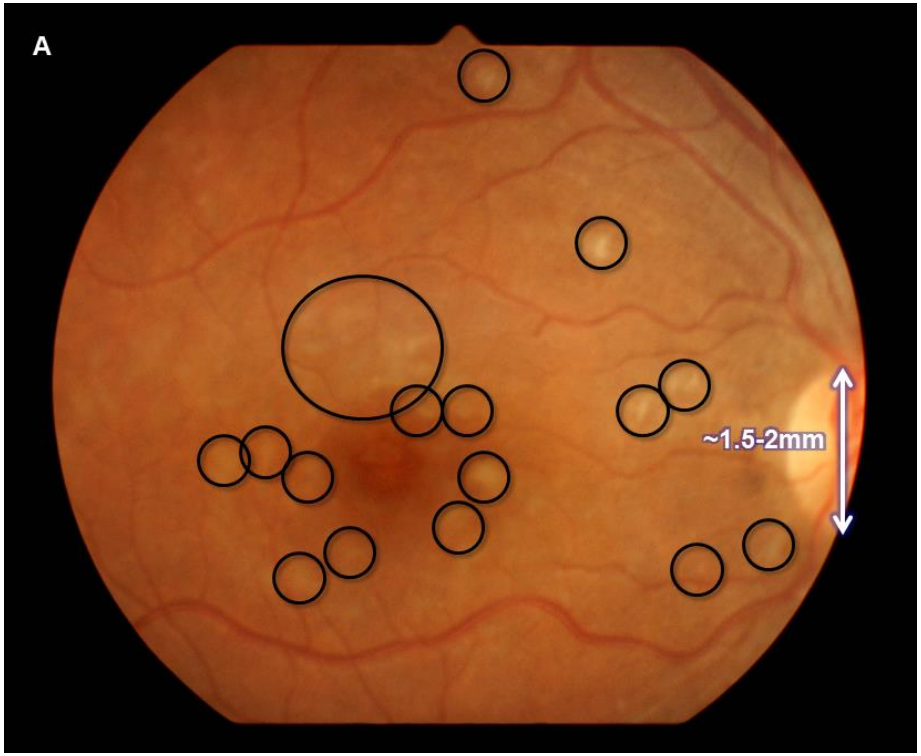
Tropical Medicine and International Health (2014); 19 (Suppl 1): 7–131

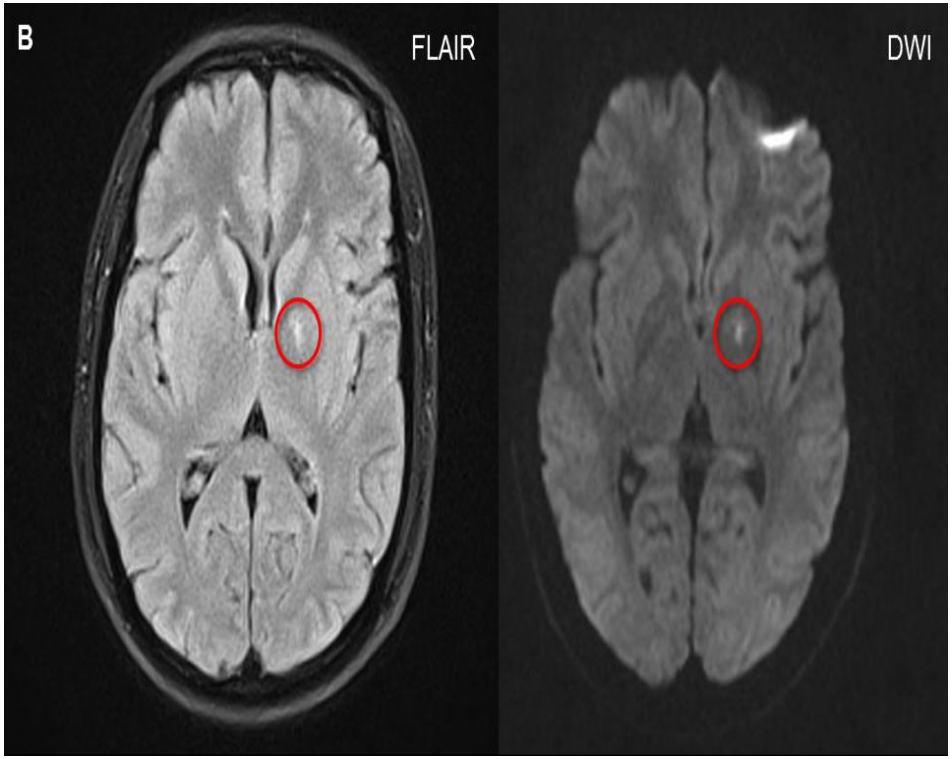


Retinal appearance in a child with cerebral malaria

Fundus photographs of a patient with severe malaria

Abu Sayeed (2011).

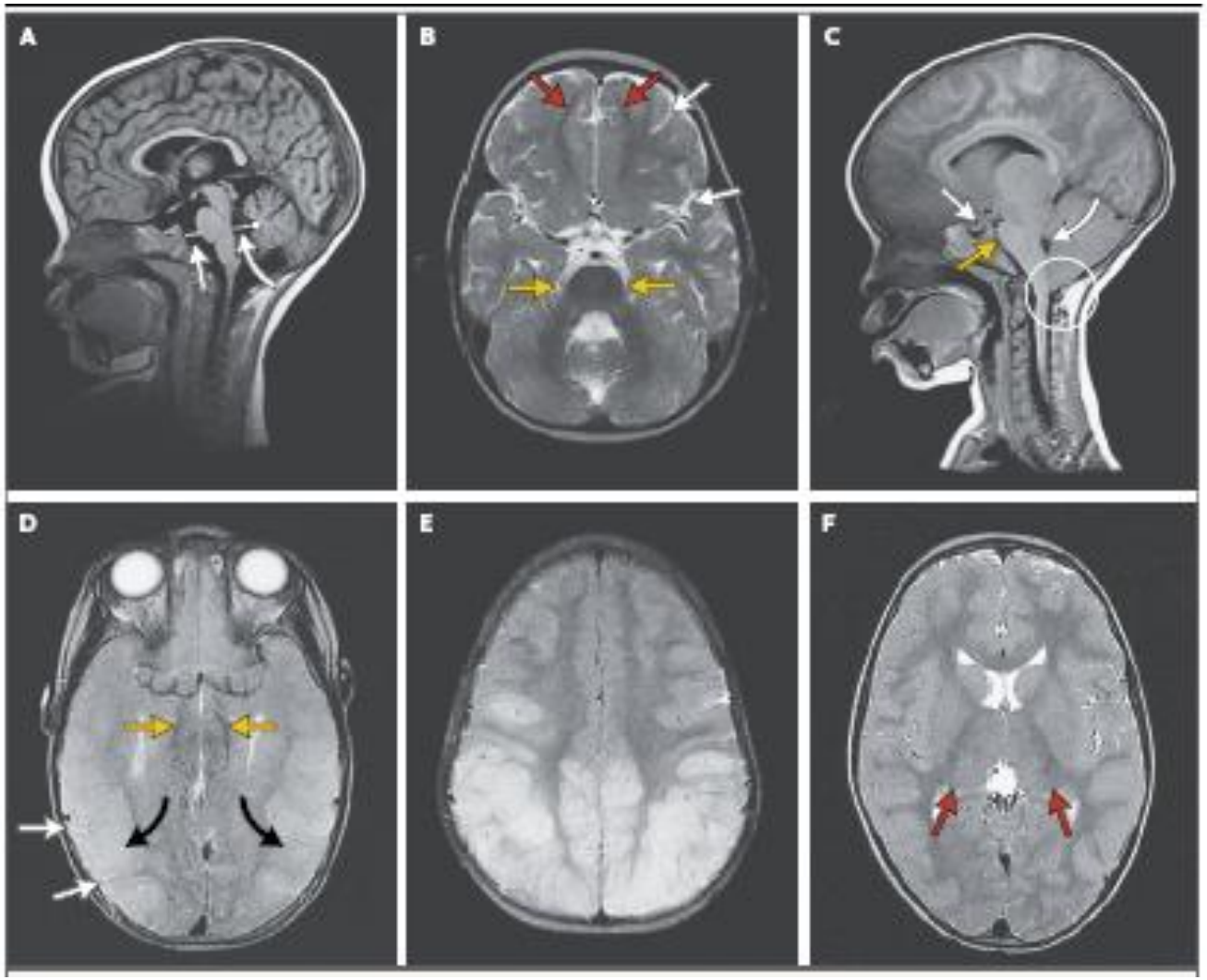




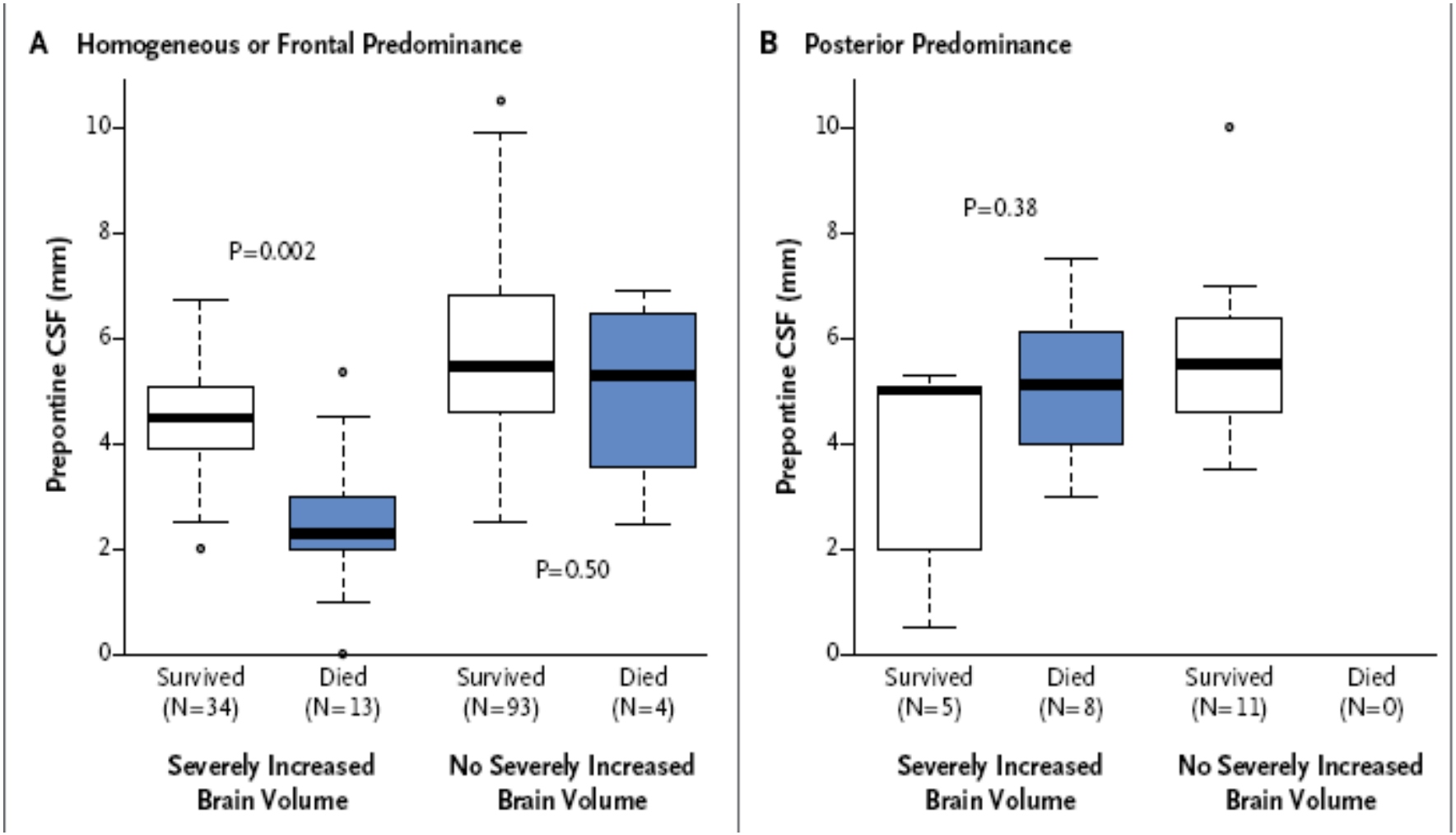
Retinal photograph and MRI from patient with cerebral malaria (GCS=8 on enrollment), hyperlactaemia and 98% sequestered biomass. A. the retina has typical lesions of retinal whitening (black circles) in the macula and fovea. Using the vertical optic disc diameter (white) as reference, each lesion of whitening is estimated at around 0.2-0.5mm diameter. B on MRI the only abnormality was high signal in the globus pallidus on T2/FLAIR (left) and DWI (right).

Brain Swelling and Death in Children with Cerebral Malaria

Ref: Karl B. Seydel, n engl j med 372;12 nejm.org march 19, 2015

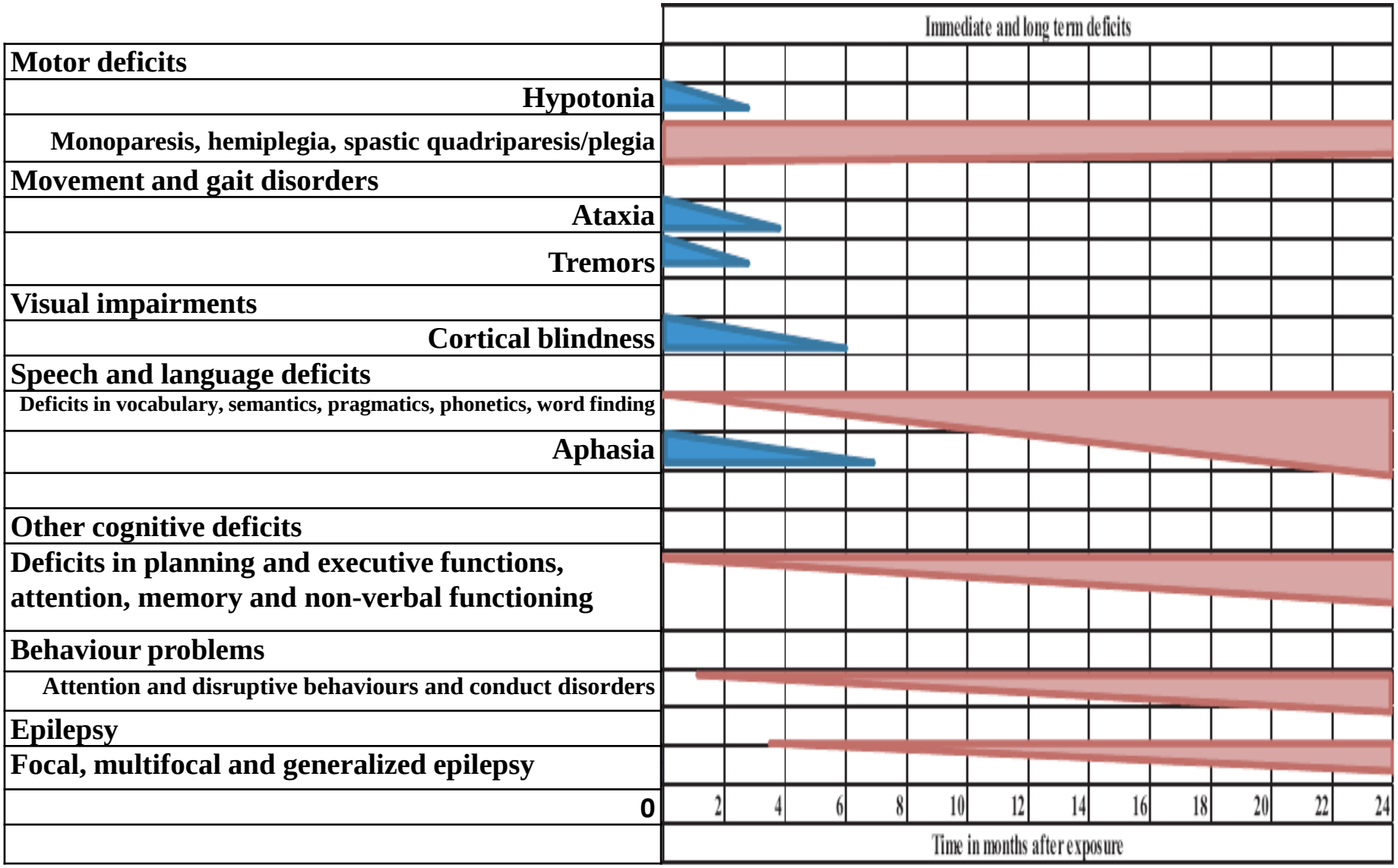


MRI Features Associated with a Fatal Outcome in Children with Retinopathy-Positive Cerebral Malaria



NEJM; 372;12 March 19, 2015

Manifestations and resolution of sequelae of cerebral malaria in children



Tropical Medicine and International Health (2014); 19 (Suppl 1): 7–131

Cerebral malaria as a risk factor for the development of epilepsy and other long-term neurological conditions: a meta-analysis

Stephanie S. Christensen and Guy D. Eslick

- **Risk of epilepsy (OR 4.68, 95% CI 2.52–8.70).**
- **Risk of intelligence quotient (IQ) impairment (OR 4.72, 95% CI 0.78–28.49).**
- **Risk of neurodisabilities (OR 16.16, 95% CI 1.34–195.45).**
- **Risk of behavioural disorder (OR 8.47, 95% CI 2.75–26.04).**

Trans R Soc Trop Med Hyg 2015 ; doi:10.1093/trstmh/trv005

Treating uncomplicated *P. falciparum* malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended forms of artemisinin-based combination therapy (ACT):

- **Artemether + lumefantrine**
- **Artesunate + amodiaquine**
- **Artesunate + mefloquine**
- **Dihydroartemisinin + piperaquine**
- **Artesunate + sulfadoxine–pyrimethamine (SP)**

(Strong recommendation, high-quality evidence)

- **ACT regimens should provide at least 3 days' treatment with an artemisininderivative.**

(Strong recommendation, high-quality evidence)

Reducing the transmissibility of treated *P. falciparum* infections

- **In low-transmission areas, give a single dose of 0.25mg/kg bw primaquine withACTto patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission.**
- **Testing for glucose-6-phosphate dehydrogenase (G6PD) is not required.**

(Strong recommendation, low-quality evidence)

Treating uncomplicated *P. falciparum* malaria in special risk groups

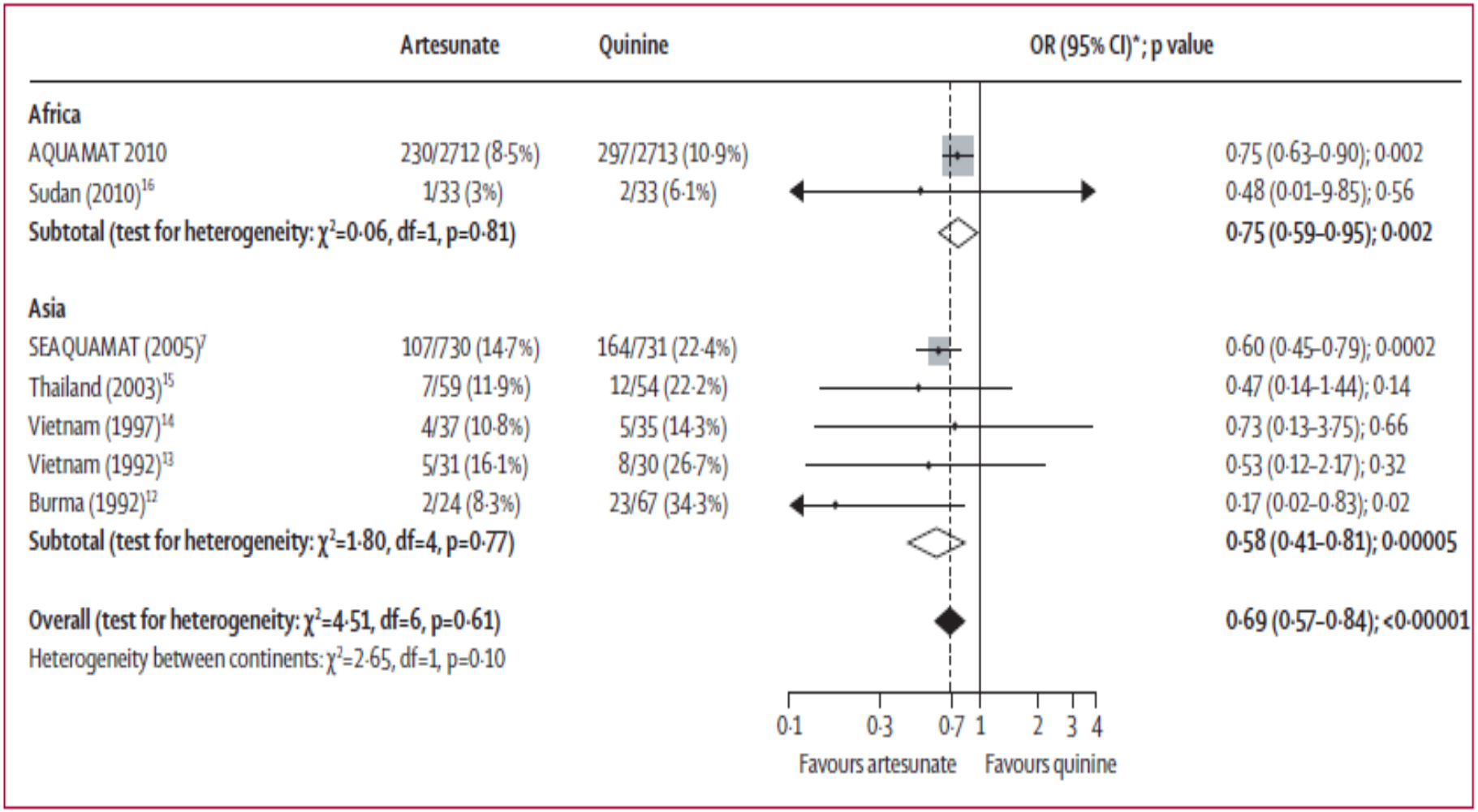
- **Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.**

  (Strong recommendation, evidence not graded)

- **People with *P. falciparum* hyperparasitaemia are at increased risk for death and should be closely monitored, in addition to receiving ACT.**

  (Good practice statement)

Meta-analysis of all randomised controlled trials that have compared parenteral artesunate and parenteral quinine in severe malaria



Lancet 2014; 383: 723–35

Treating Severe Malaria

- **Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication.**

(Strong recommendation, high-quality evidence)

- **Once a patient has received at least 24 h of parenteral therapyand can tolerate oral therapy, complete treatment with 3 days of ACT.**
- ***(Strong recommendation, high-quality evidence)***
- **Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.**

(Strong recommendation based on evaluation of pharmacokinetics)

- **If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.**

(Conditional recommendation, low-quality evidence)

Treating cases of suspected severe malaria pending transfer to higher-level facilities (pre-referral treatment)

- **Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate,and refer to an appropriate facility for further care. Use intramuscular artemether or quinine if artesunate is not available.**

  (Strong recommendation, moderate-quality evidence)

- **Where intramuscular injections are not available, treat children < 6 years with a single rectal dose of artesunate, and refer immediately to an appropriate facility for further care.**

  (Strong recommendation, moderate-quality evidence)

Exposure to artemether-lumefantrine (Coartem®) in first trimester pregnancy in an observational study in Zambia

- **294 1st TM exposure- 150 A-L, AL-SP 9, SP&/or Quinine 135.**
- **Perinatal mortality 4.4 % vs 3.9%.**
- **At delivery, gestational age, length-head circumference- same.**
- **Overall development and neurodevelopment at 14 weeks and 12 months- similar.**

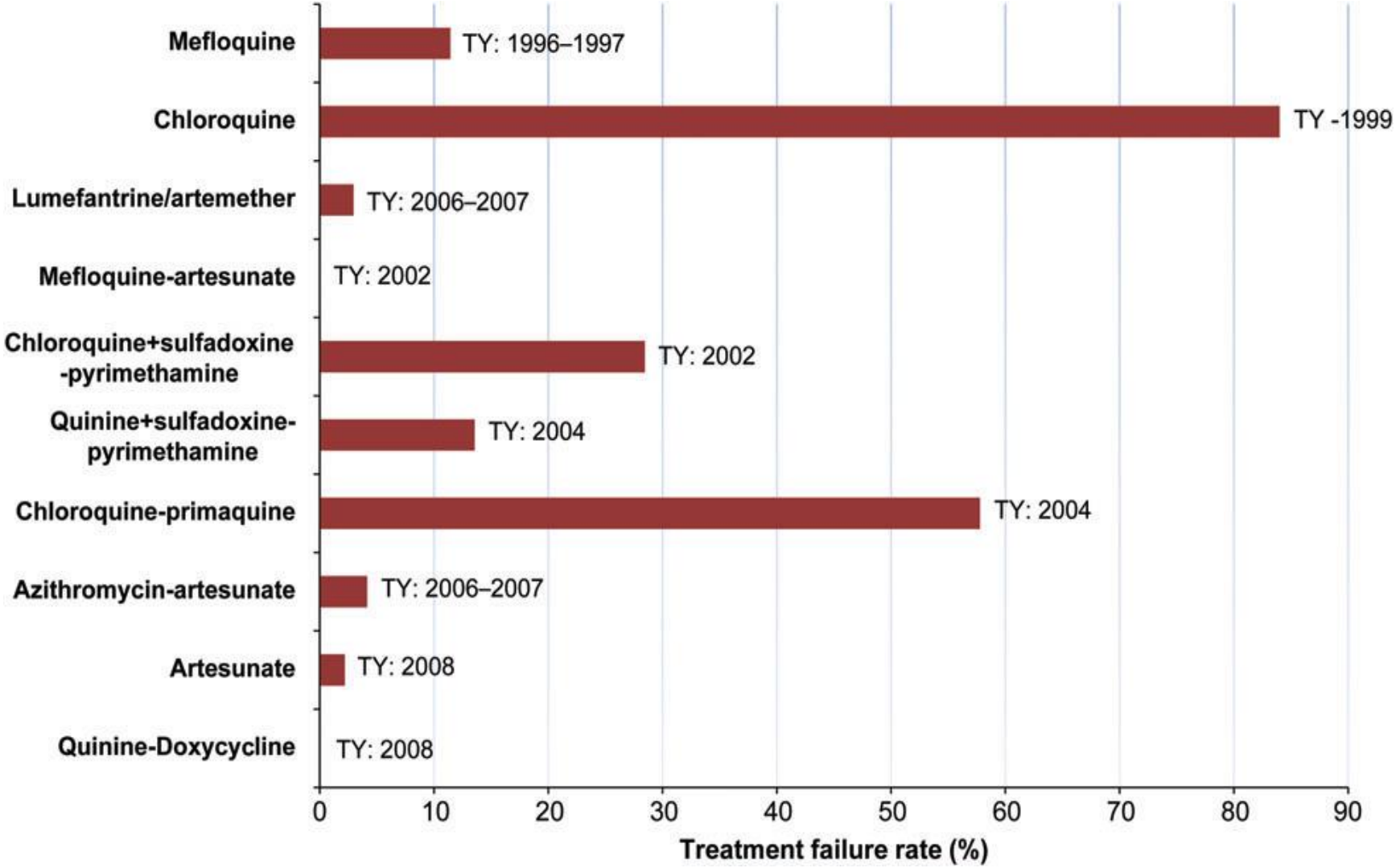
Christine Manyando et al. Malaria Journal (2015) 14:77

The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data

- **61 studies 1998- 2012, 14327 patients.**
- **PCR adjusted treatment success 97.6% 28d, 96% 42d Follow up.**
- **Asia- 10-15 kg children, 91.7%.**
- **Africa- malnourished children 1-3 y, 94.3%.**

WWARN, AL Dose Impact Study Group; The Lancet, March 16, 2015

Antimalarial drug resistance in trials with >28-day follow-up and the proportion (%) of treatment failures in Bangladesh.

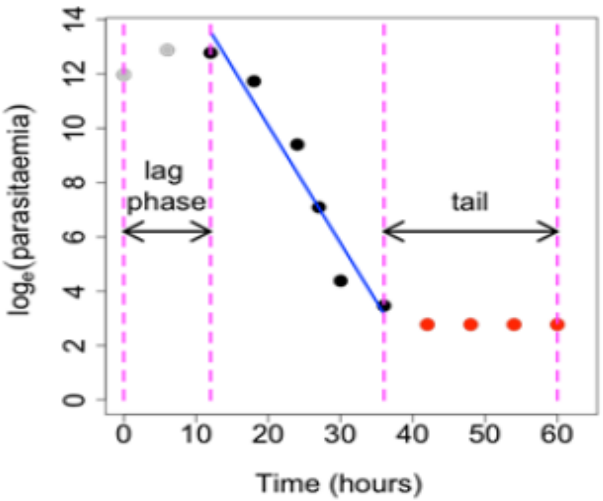


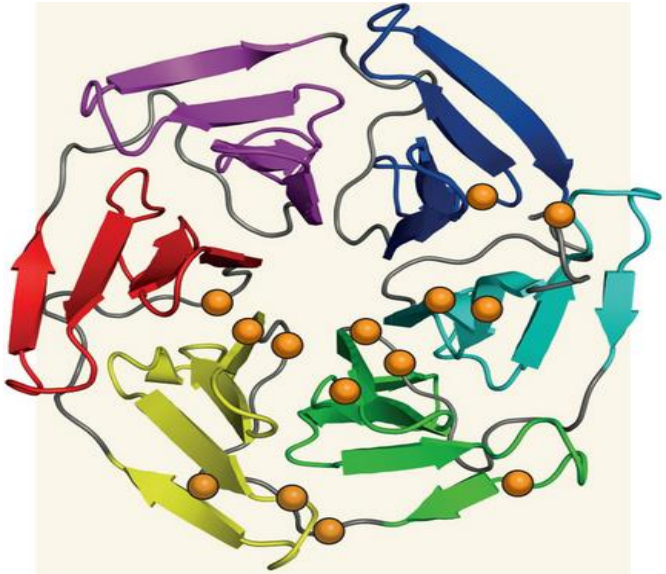
Trans R Soc Trop Med Hyg doi:10.1093/trstmh/trt088

TRAC Artemisinin Resistance

Primary endpoint = parasite clearance half-life

- **Parasite clearance is estimated for each individual patient based on the linear part of the log parasitaemia-time profile.**
- **Convenient way to explain clearance is as the half-life of the parasite clearance slope.**

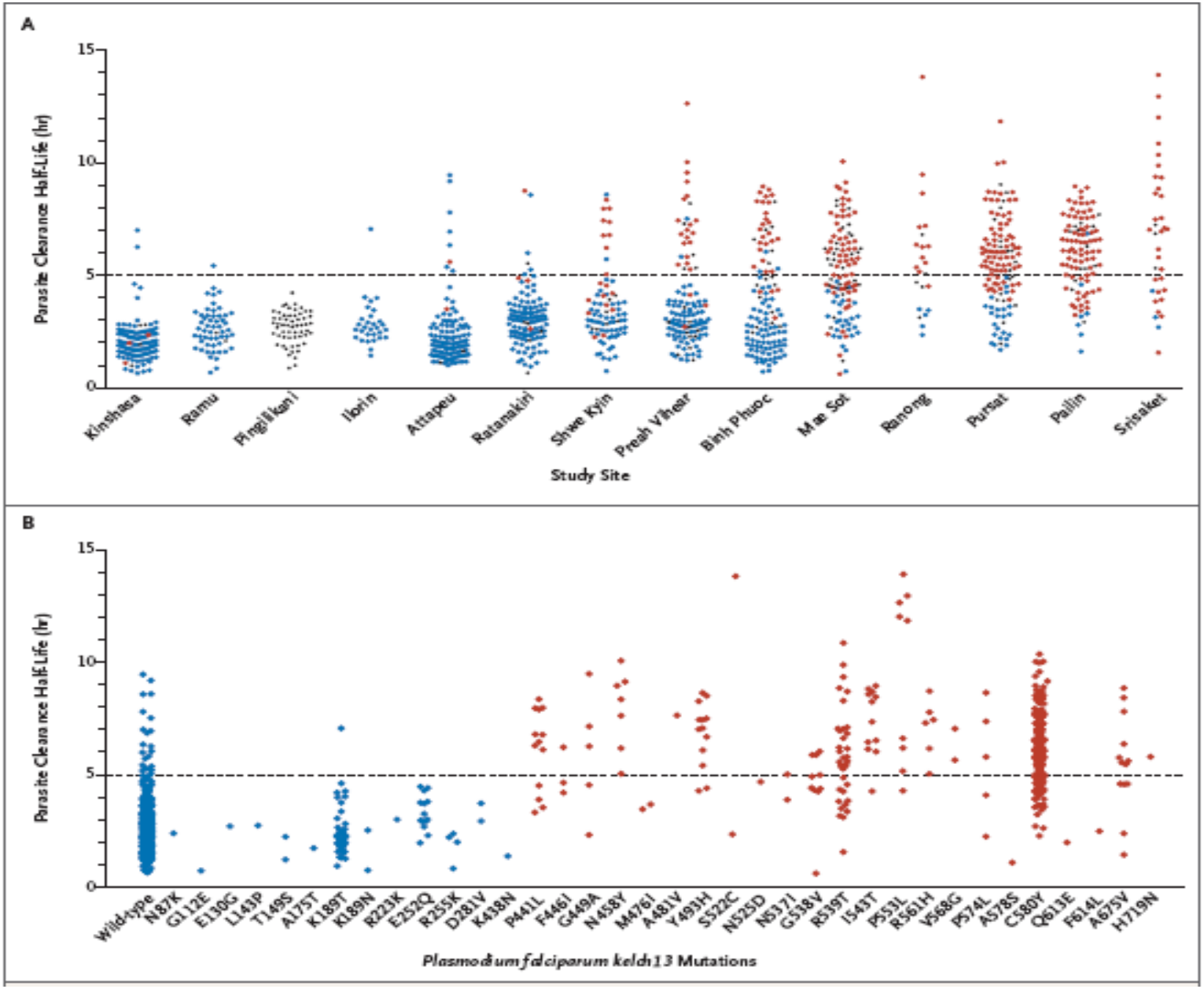




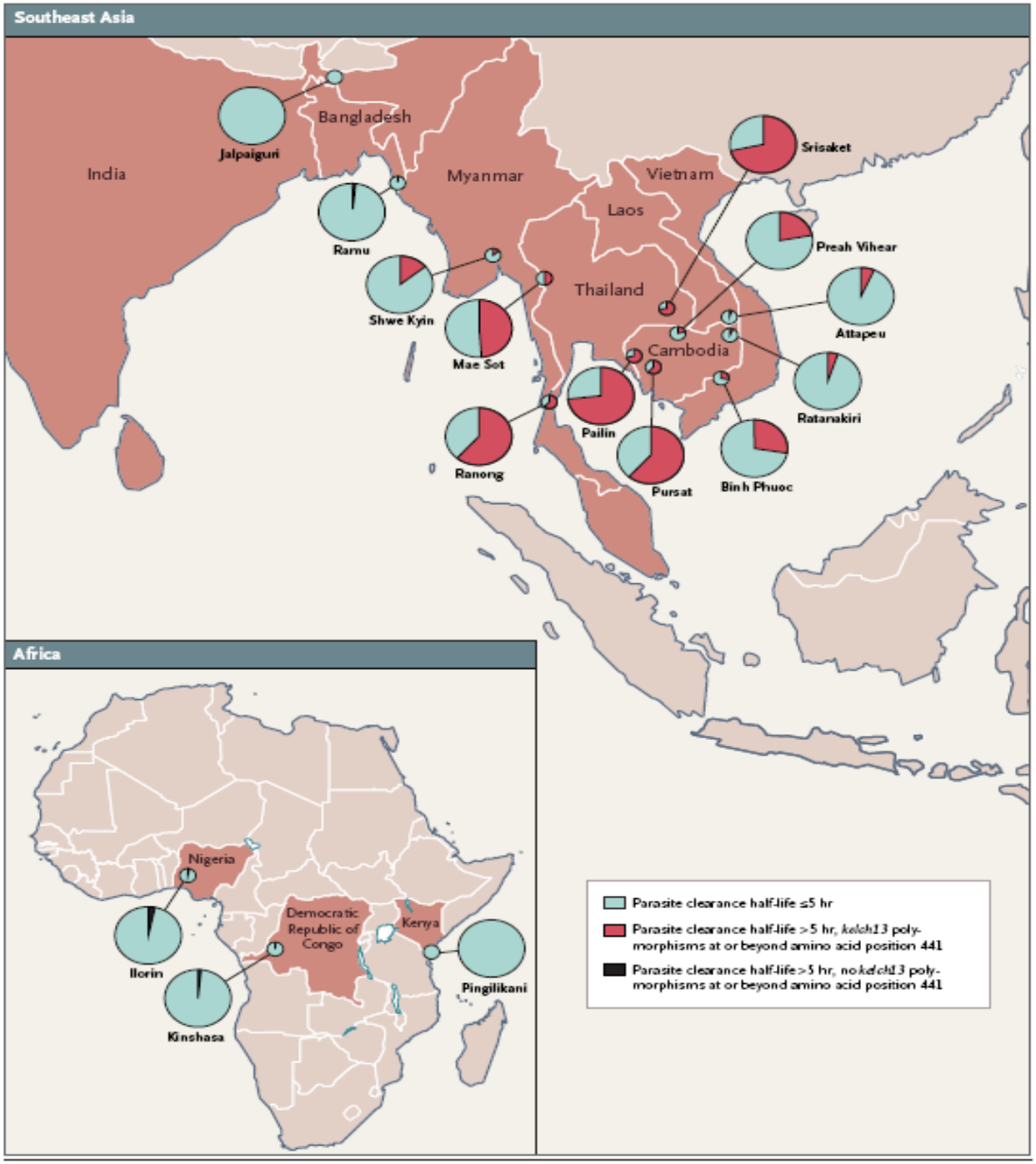
Nature 2014: 505, 30–31

Propeller Mutations

Distribution of Parasite Clearance Half-Lives.

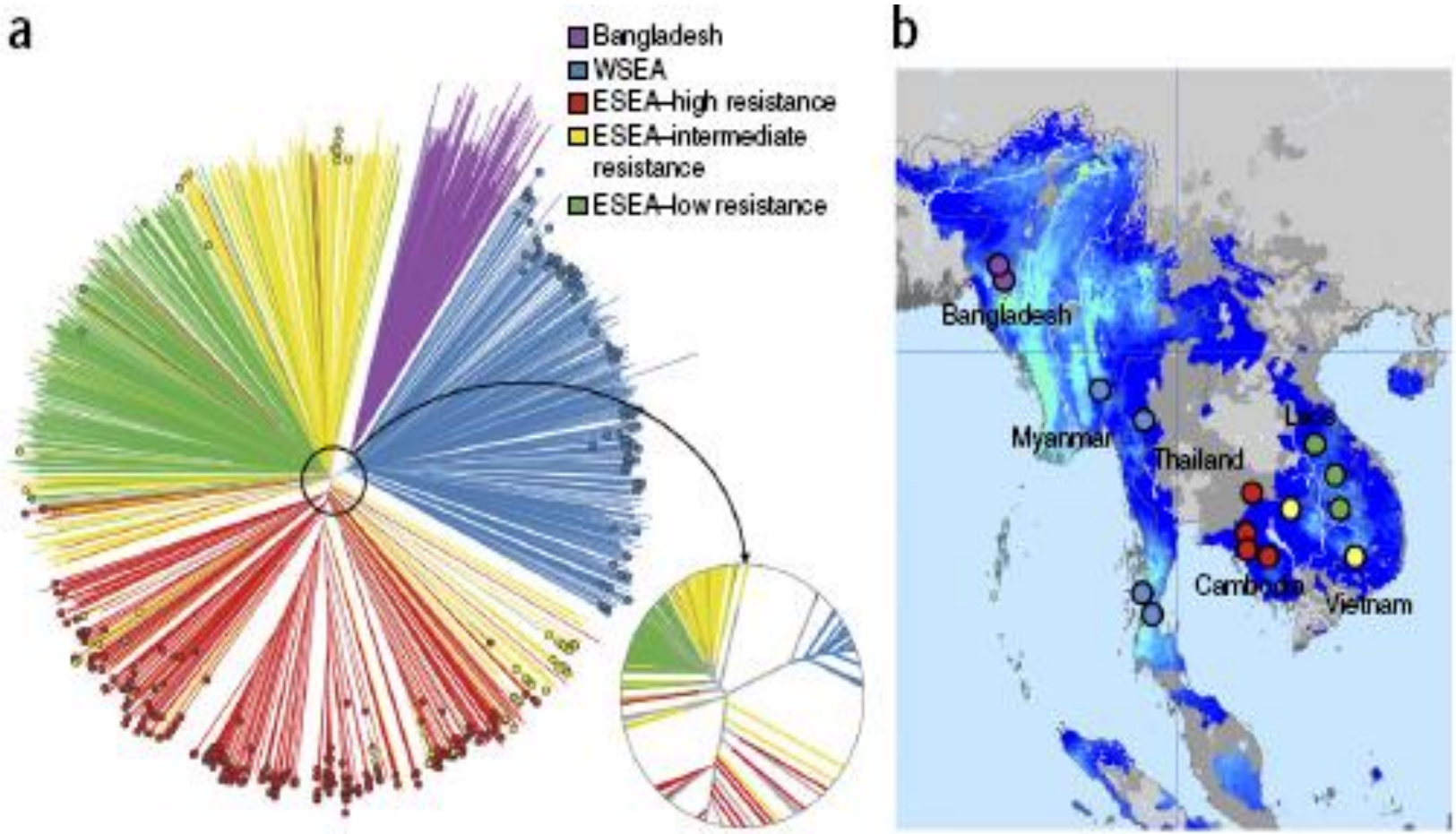


NEJM, 2014; 371 (5): 411-423



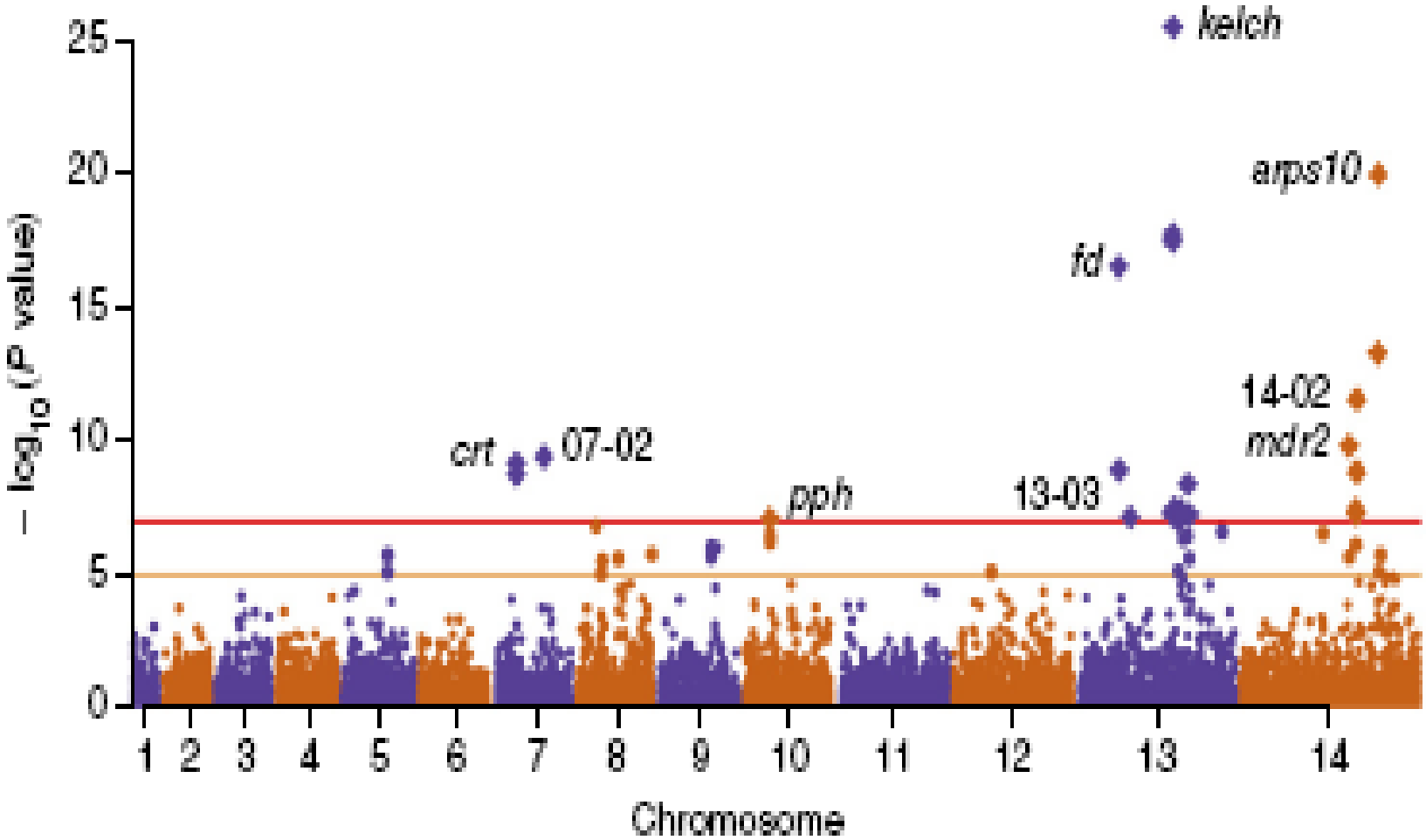
NEJM, 2014; 371 (5): 411-423

Population structure and distribution of *kelch13 mutants in Southeast Asia.*



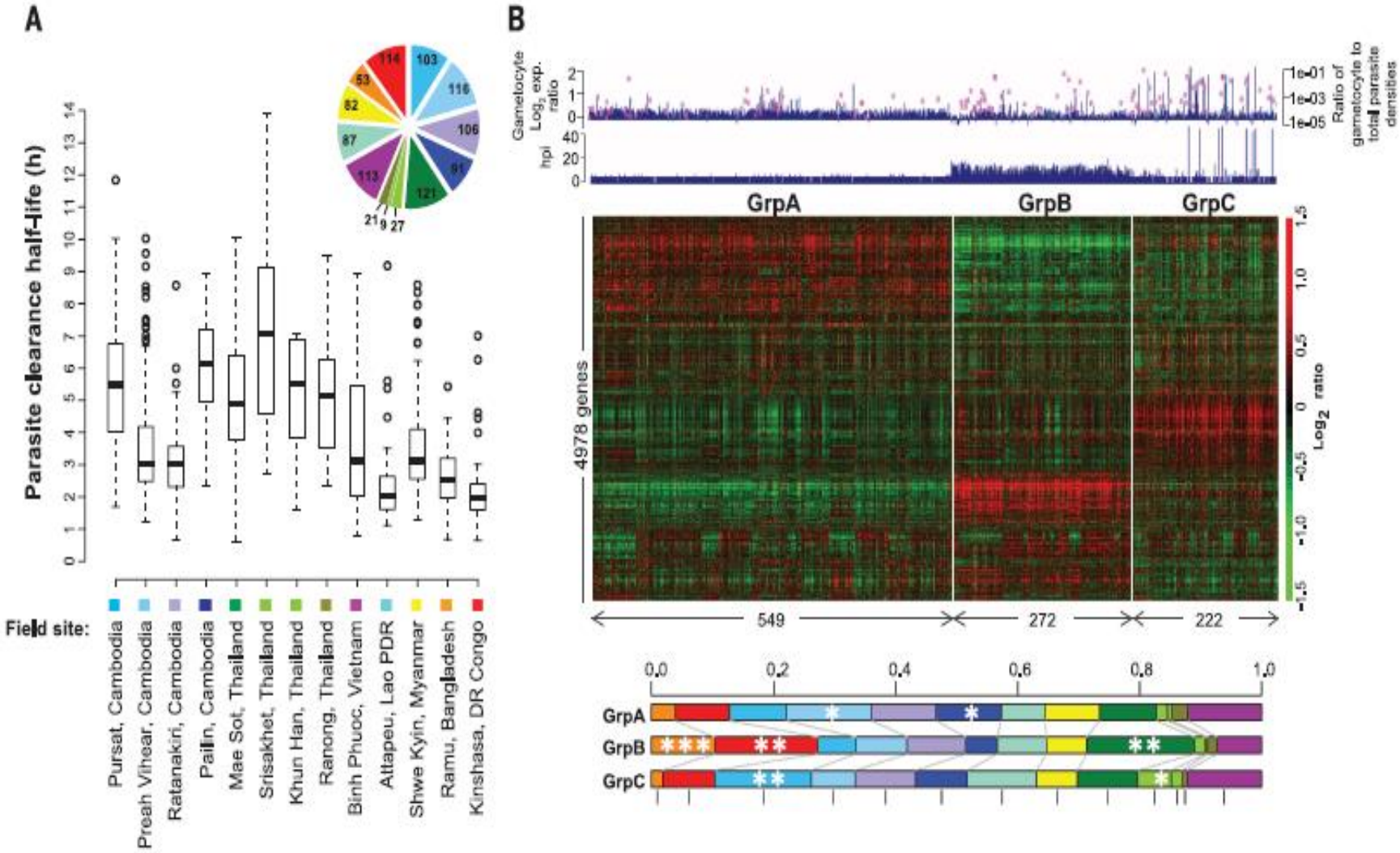
Nature Genetics; 47 (3): 226-234

Manhattan plot showing the significance of SNP association in the GWAS



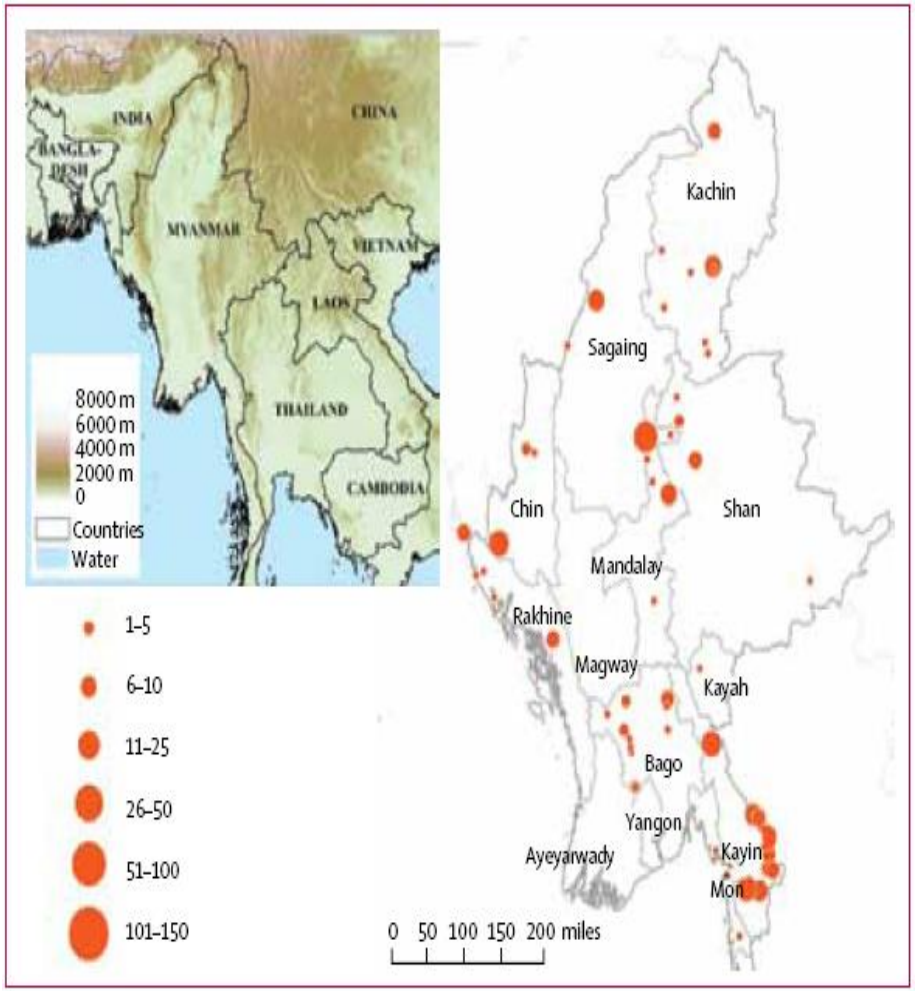
Nature Genetics; 47 (3): 226-234

Artemisinin response and transcription profiles of P. falciparum isolates from patients with acute malaria.



Science, 2015; 347: 431-435

Location of sampling sites, sample sizes, and administrative states and regions of Myanmar, and a relief map of southeast Asia



	Total samples	Samples with propeller mutation*	Proportion (%)
Myanmar			
Bago	52	0	0 (0–6·9)
Chin	62	2	3·2 (0·9–11)
Kachin	70	26	37·1 (26·8–48·9)
Kayah	2	2	100 (34·2–100)
Kayin	288	137	47·6 (41·9–53·3)
Mandalay	181	43	23·8 (18·1–30·5)
Mon	8	3	37·5 (13·7–69·4)
Rakhine	29	2	6·9 (1·9–22)
Sagaing	46	21	45·7 (32·2–59·8)
Shan	21	14	66·7 (45·4–82·8)
Bangladesh			
Chittagong	25	0	0 (0–13·3)
Thailand			
Tak	156	121	77·6 (70·4–83·4)
Total	940	371	39·5 (36·4–42·6)

Data in parentheses are 95% CI. We calculated confidence intervals with the Wilson Test (without continuity correction). * After aminoacid 440.

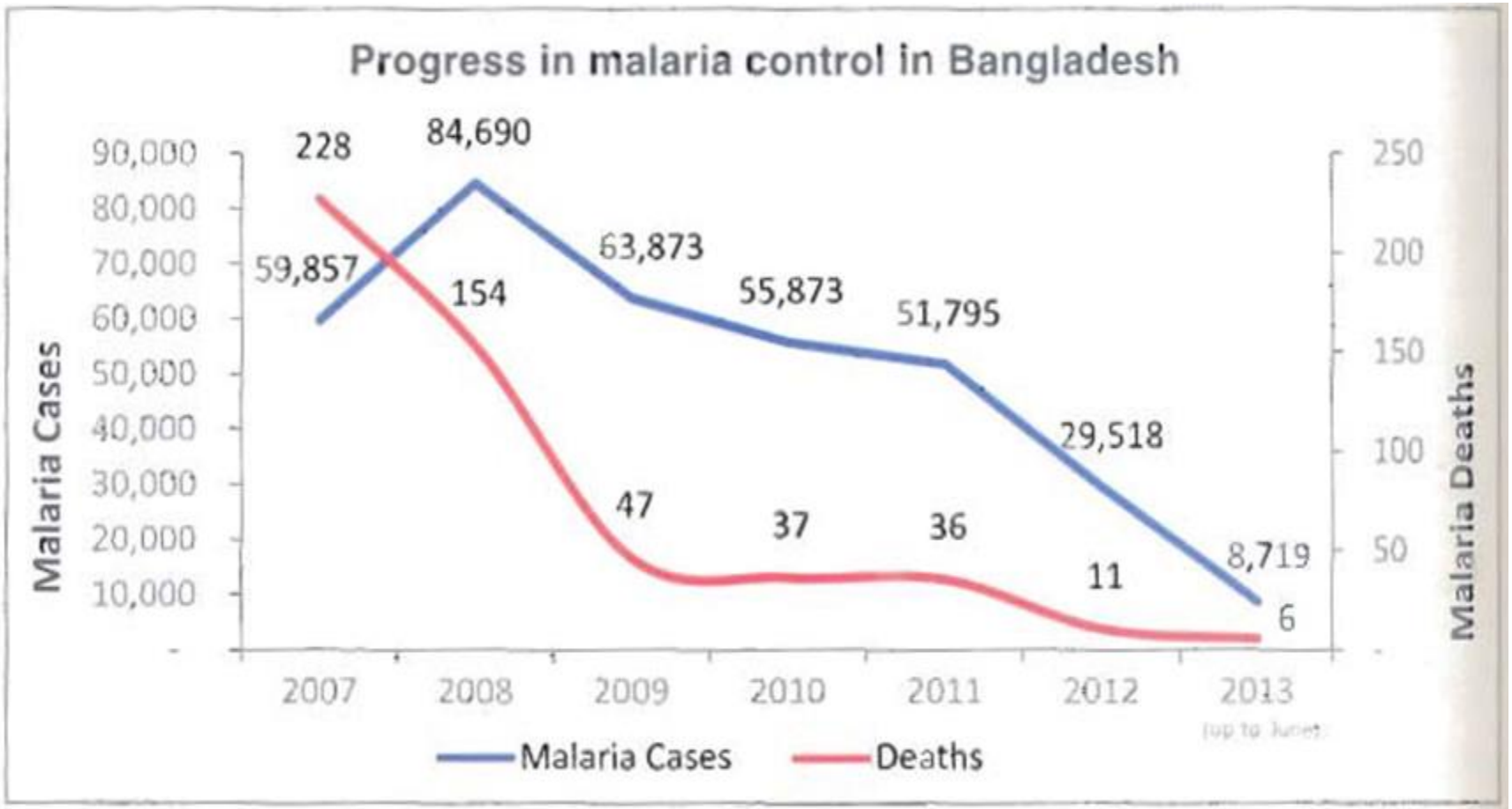
Number of samples per region and proportion with mutations in the propeller domain of K13

www.thelancet.com/infection Published online February 19, 2015 http://dx.doi.org/10.1016/S1473-3099(15)70032-0

Some Future Directions

- **Mapping of AM resistance- molecular surveillance, K13 gene.**
- **Treatment of Artemisinin resistant falciparum malaria TRAC II:**
  - **Uncomplicated malariaTriple ACTs: A-L-AQ, DHAPPQ.**
  - **Severe malaria: Inj AS+ Inj Quinine.**
- **A potential single dose of cure for malaria:**
  - **MMV390048, aminopyridine class + a partner drug, Phase I study ongoing.**
- **RCT- safety & efficacy of ACT in 1st TM pregnancy.**
- **Assessment of high dose ACT in younger age and in manourished children.**

Malaria



Trend of Malaria cases and deaths (2007-2013 June) in 13 endemic districts of Bangladesh

Final Version

Malaria National Strategic Plan
2015-2020

Creating Sustainable Impact

National Malaria Control Programme (NMCP)
Communicable Disease Control Division
Directorate General of Health Services
Ministry of Health & Family Welfare
Bangladesh

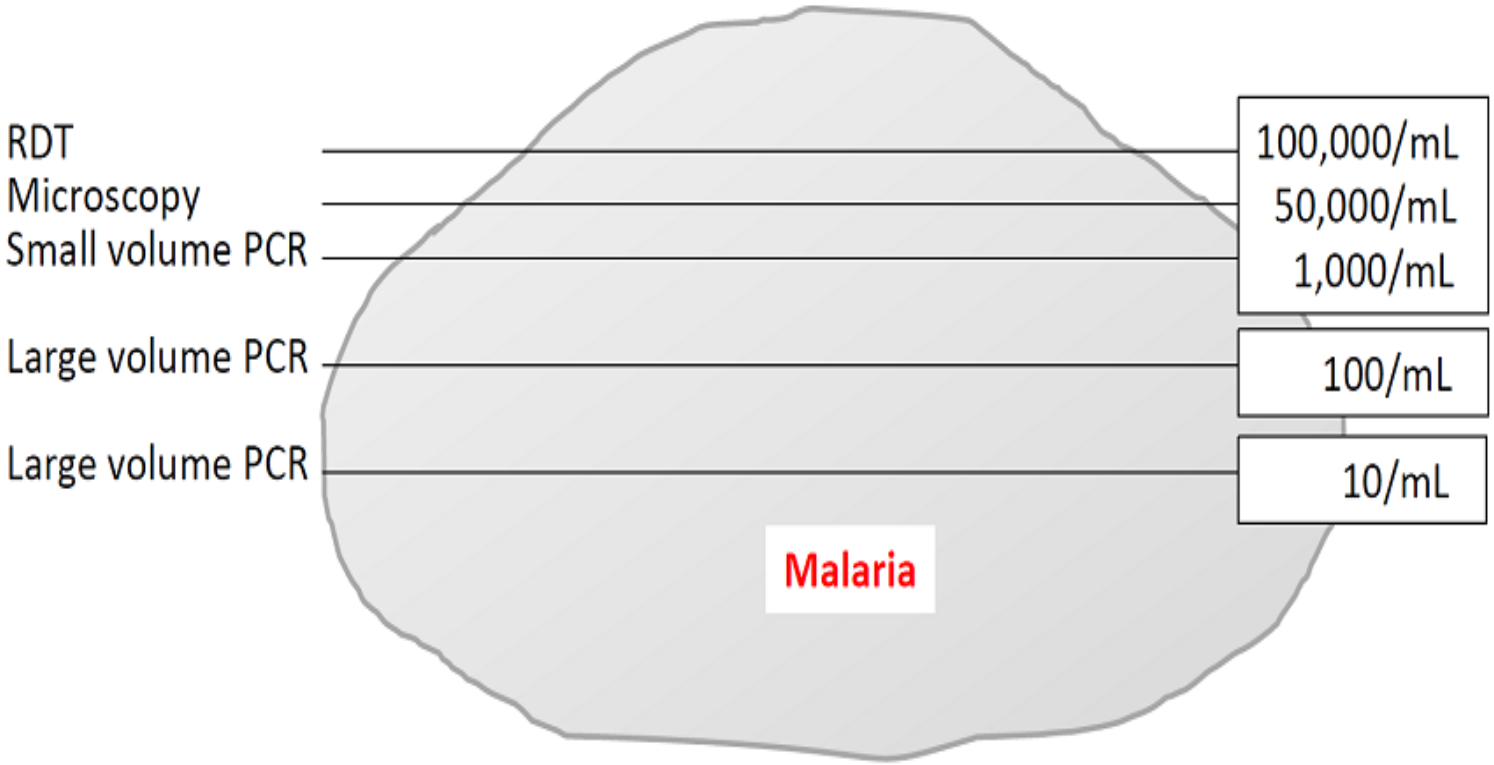
National Malaria Control Strategy

Vision: Malaria-free Bangladesh

Goal: By 2020, to have achieved ‘zero indigenous transmission’ and ‘zero death’ aiming malaria elimination in Bangladesh

How much malaria can we detect?

Effects of different sensitivities of detection on estimated prevalence of malaria



Thank You