

# Drug resistant malaria: a risk assessment



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World Health  
Organization

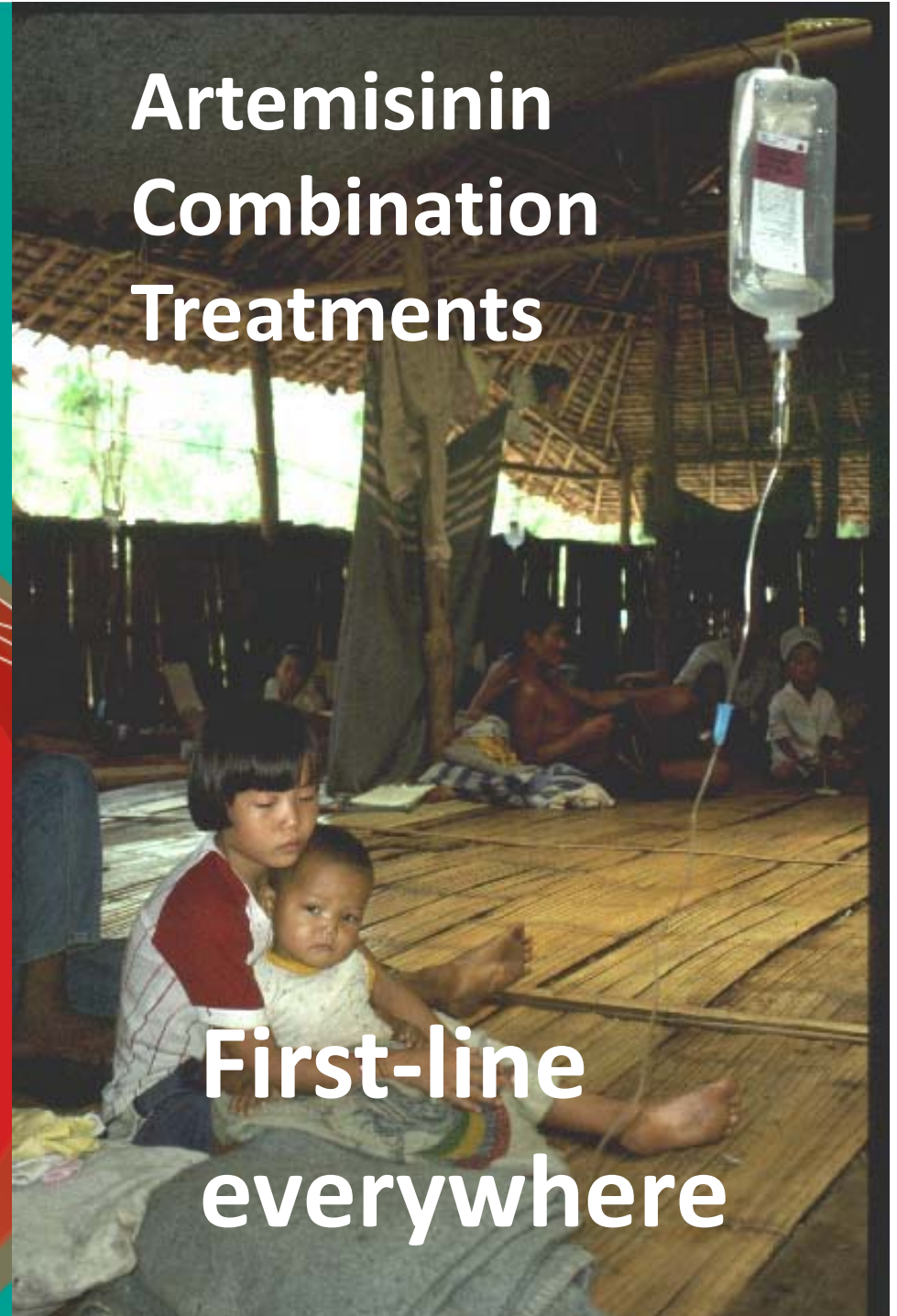
GUIDELINES  
FOR THE TREATMENT  
OF MALARIA

2006



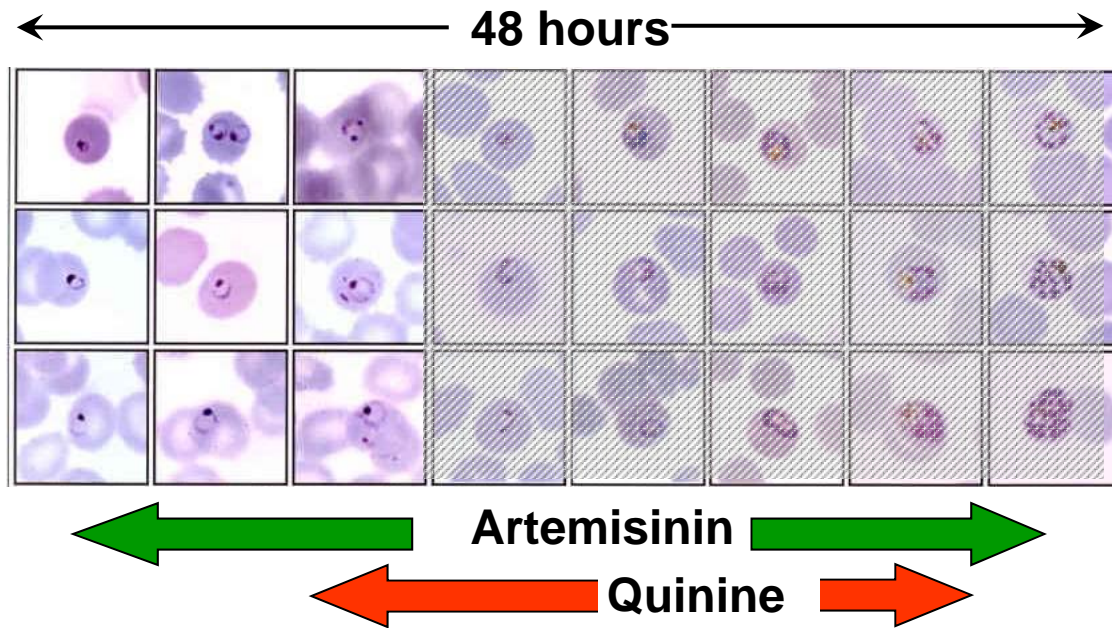
Artemisinin  
Combination  
Treatments

First-line  
everywhere



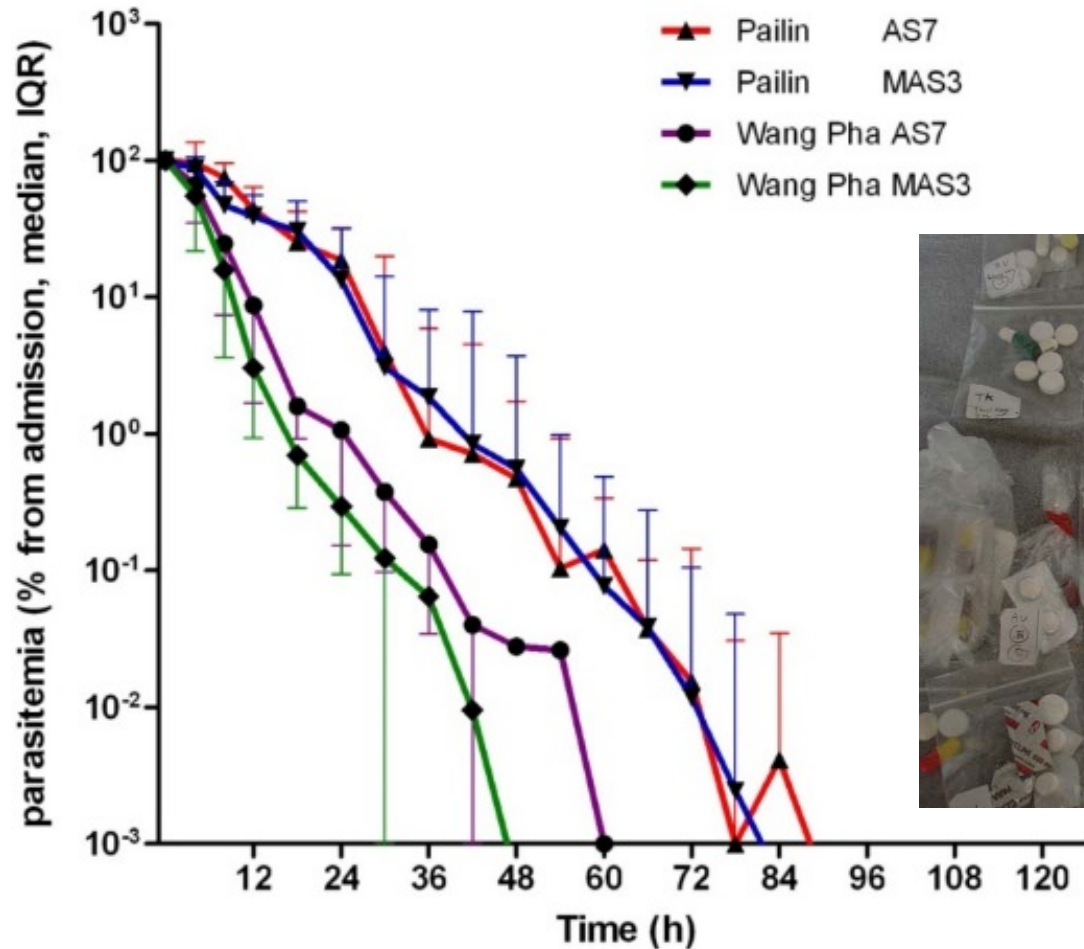
# Artemisininins

Rapid and potent action, broad stage specificity, gametocytocidal



# Artemisinin resistance – slow parasite clearance

First recognised in Western Cambodia



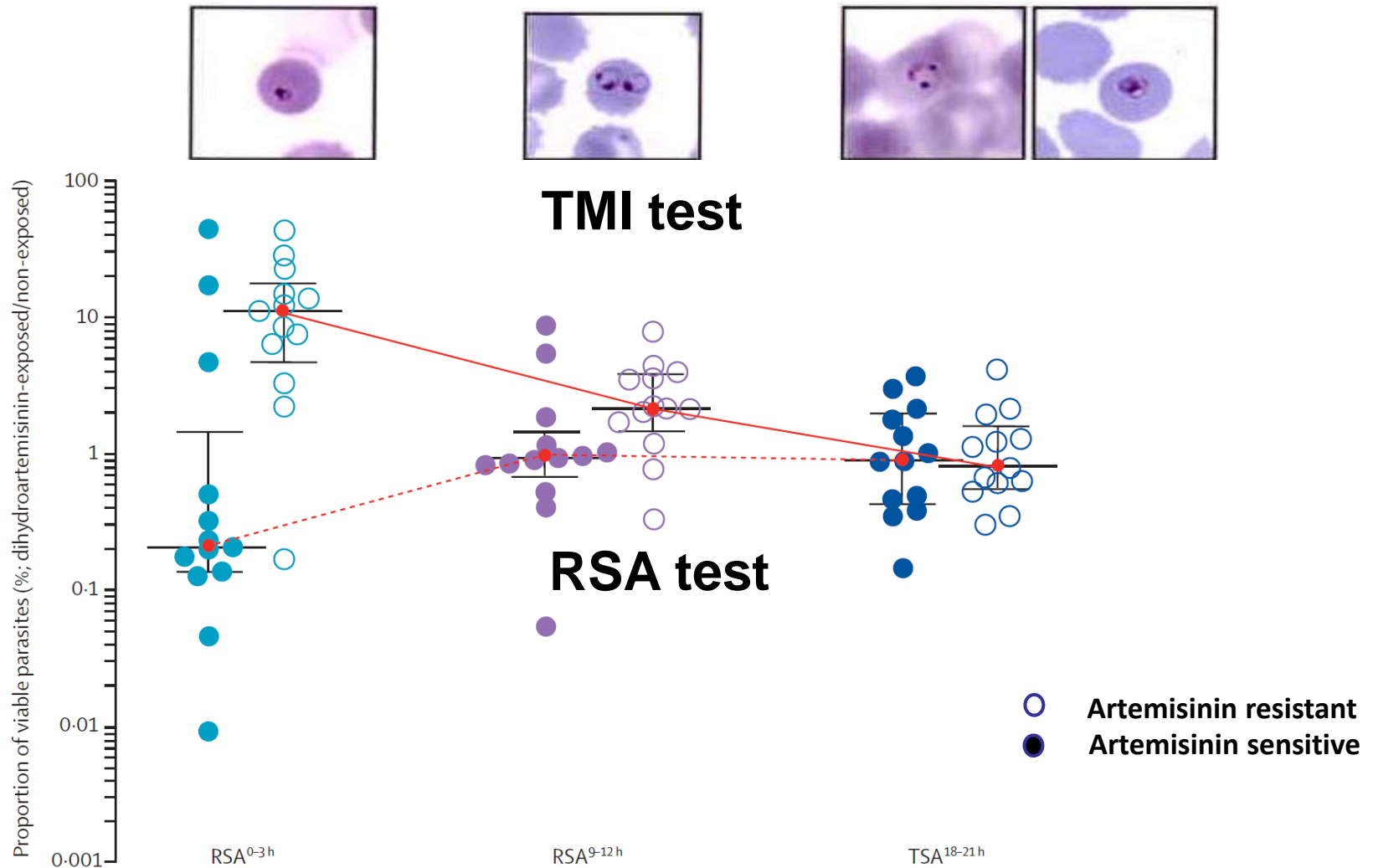
Dondorp et al. *N Engl J Med* 2009



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# Artemisinin resistance is mainly in the early ring stage



Witkowski et al.  
*Lancet Infect Dis* 2013



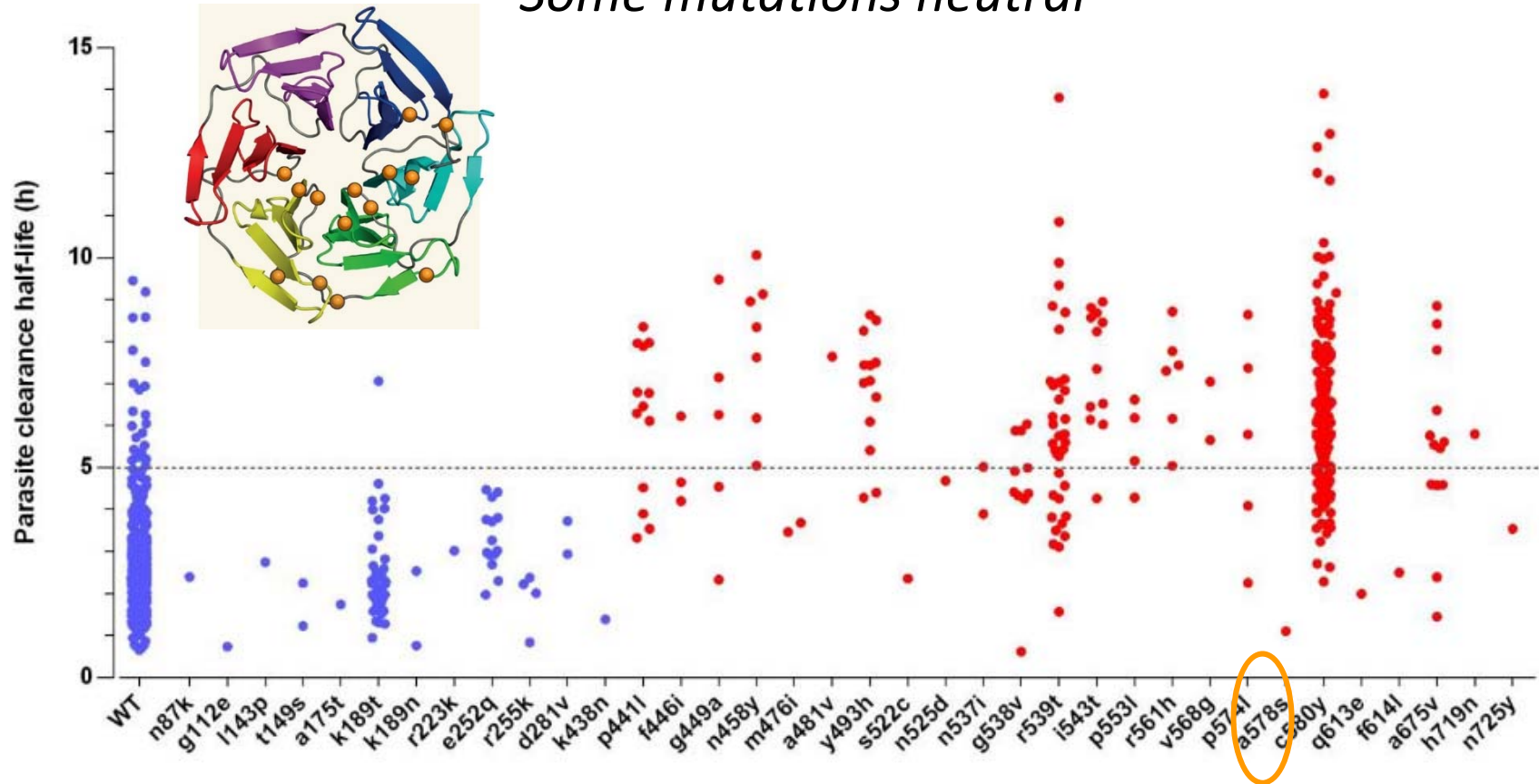
wellcome trust  
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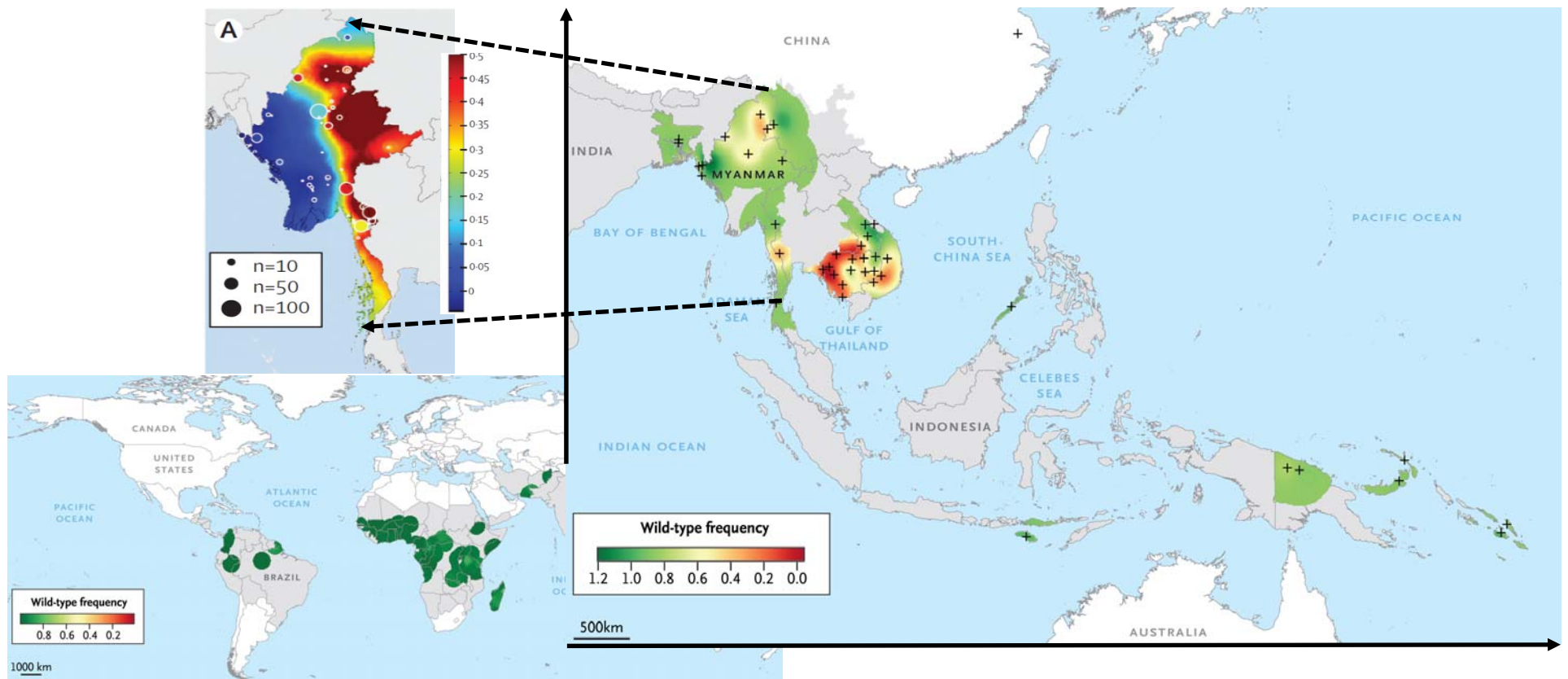
Chotivanich et al.  
*AAC* 2014

# ≥ 75 mutations in the propeller region of *Pf*Kelch 13

*Association with slow clearance not uniform.  
Some mutations neutral*



# *Pf*Kelch13 mutations: geographic distribution



Menard et al. *N Engl J Med* 2016

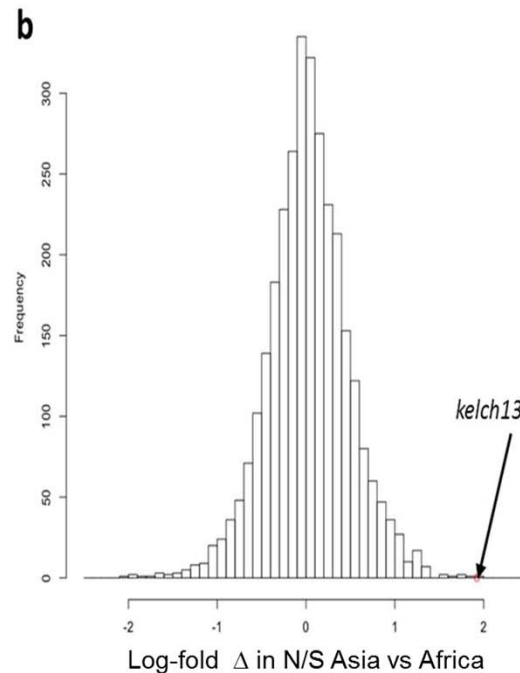
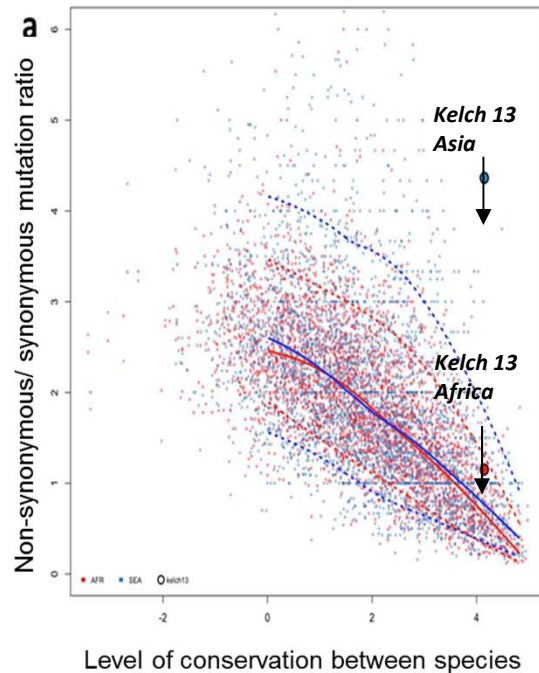


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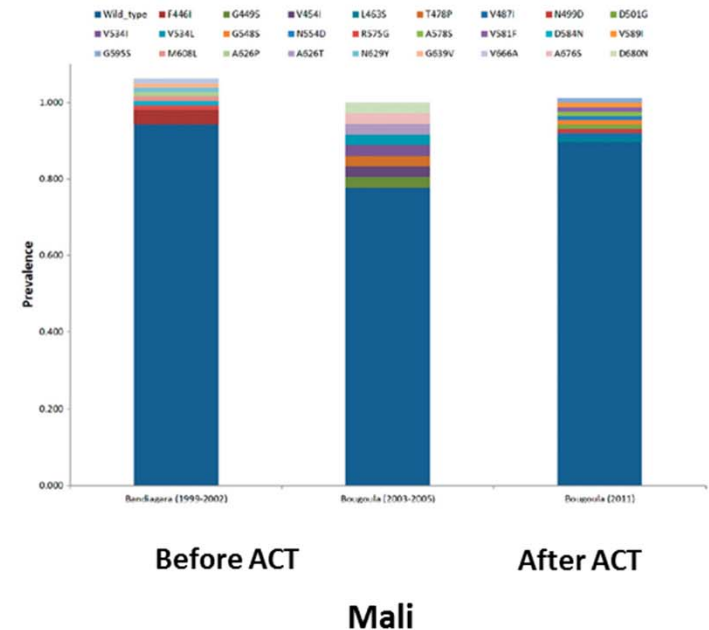


Tun et al. *Lancet Infect Dis* 2016

# *PfKelch13* in Africa: no evidence (yet) for selection



## Bougoula-Hameau and Bandiagara



Miotto et al. Nat Gen 2015



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Quattara et al.  
Am J Trop Med Hyg 2015

# Worrying report

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE



## Emergence of Indigenous Artemisinin-Resistant *Plasmodium falciparum* in Africa

Feng Lu, Ph.D.  
 Jiangsu Institute of Parasitic Diseases  
 Wuxi, China

Richard Culleton, Ph.D.  
 Nagasaki University  
 Nagasaki, Japan

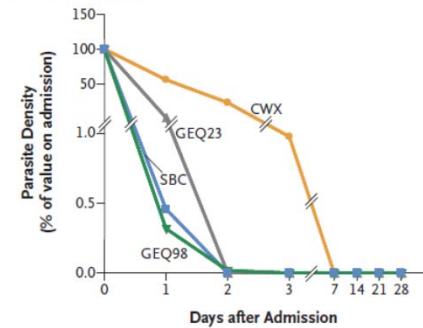
Meihua Zhang, M.Sc.  
 Shanghai East Hospital  
 Shanghai, China

Abhinay Ramaprasad, M.Sc.  
 King Abdullah University of Science and Technology  
 Thuwal, Saudi Arabia

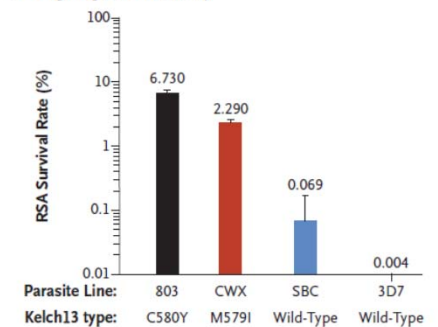
Lorenz von Seidlein, Ph.D.  
 Mahidol University  
 Bangkok, Thailand



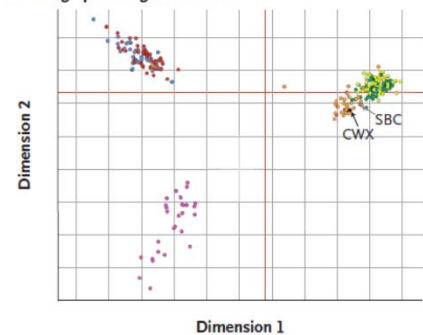
A Parasite Density



B Ring-Stage Survival Assay



C Geographic Origin of Isolates

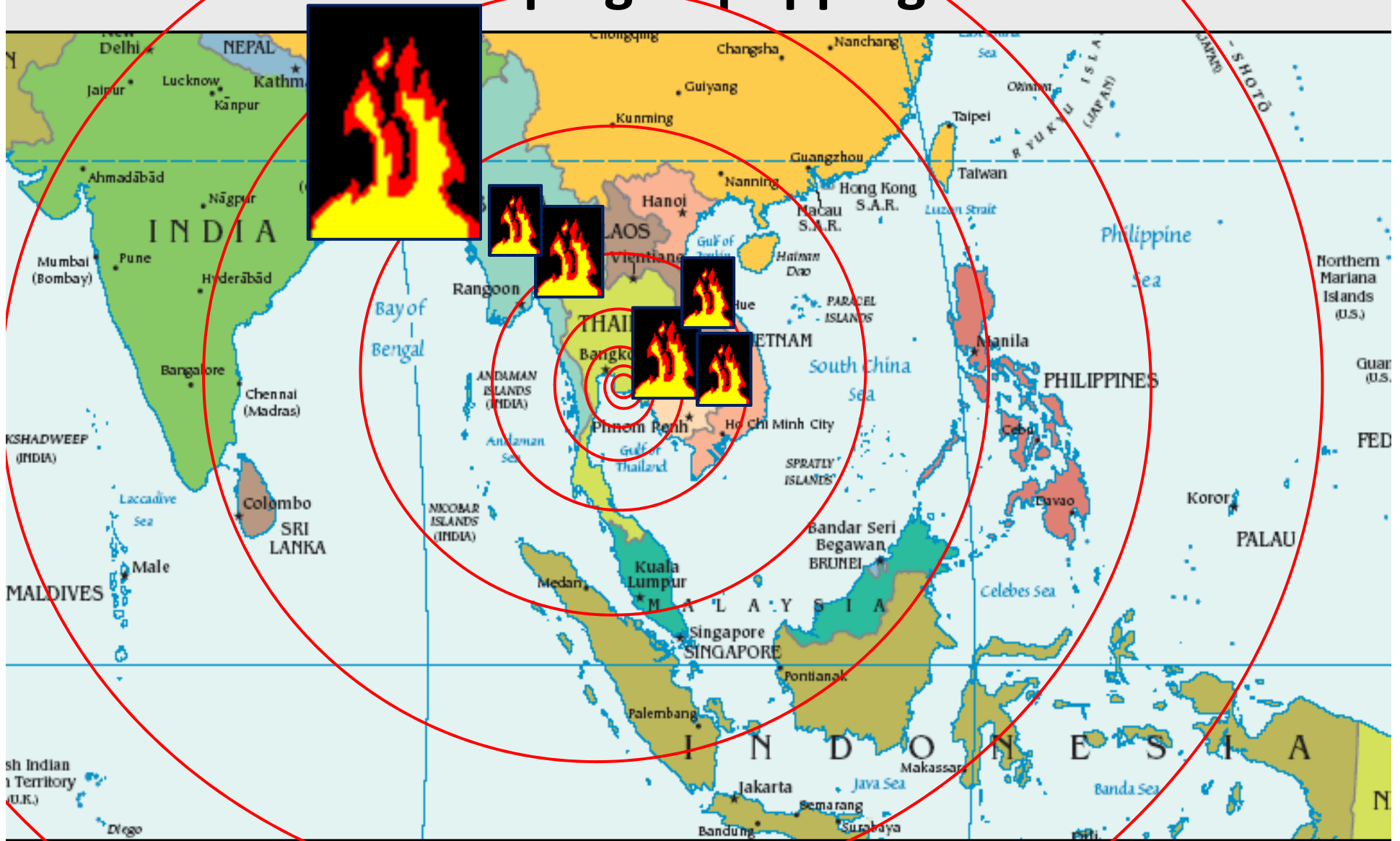


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# Jumping or popping?

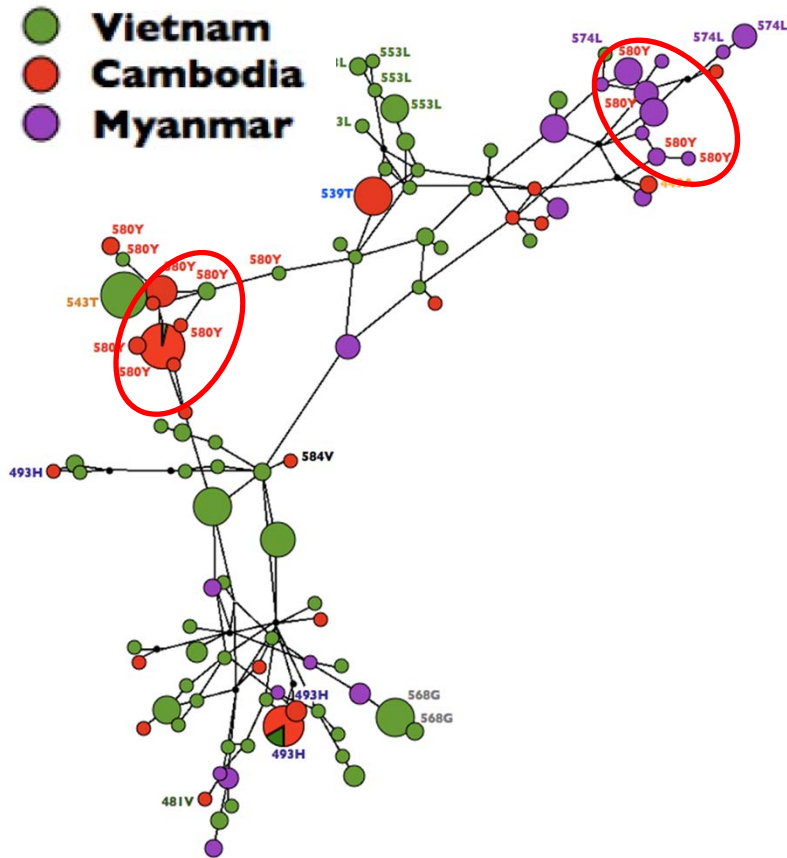


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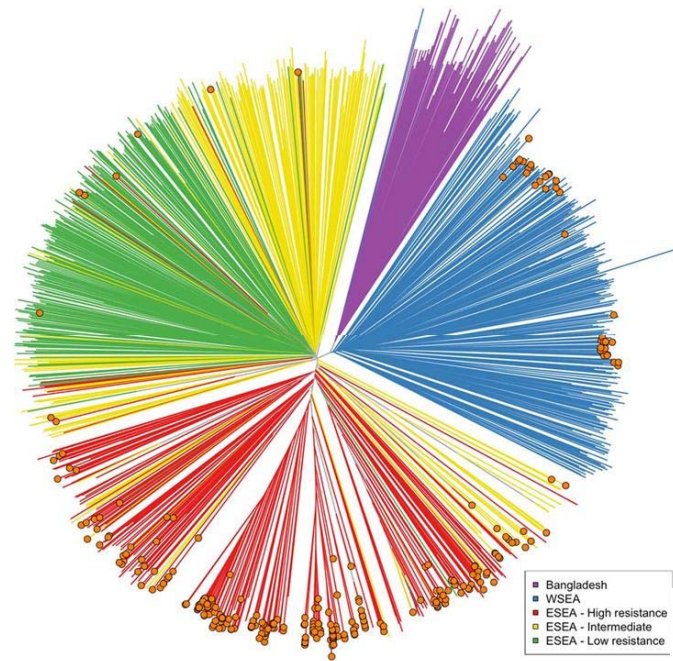


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# Multiple independent emergences of *PfKelch* mutations



Median Joining Haplotype Network of K13 Mutations and SNPs within Linkage Disequilibrium of the K13 Propeller Protein

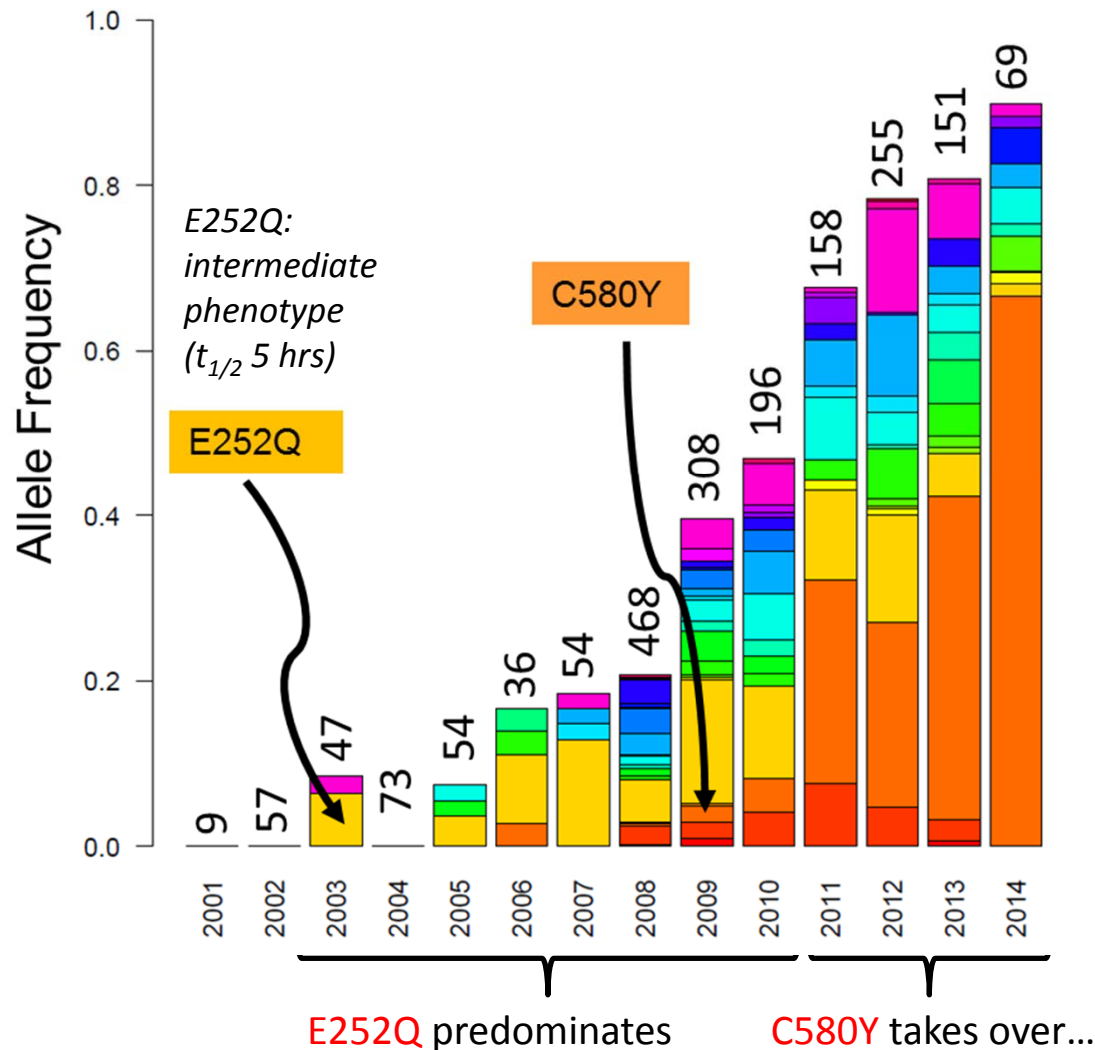


Neighbour-joining tree of samples carrying K13 SNPs

- Bangladesh
- WSEA
- ESEA - High resistance
- ESEA - Intermediate
- ESEA - Low resistance

***C580Y* mutant found in Myanmar did not spread from Cambodia -it arose independently in Myanmar**

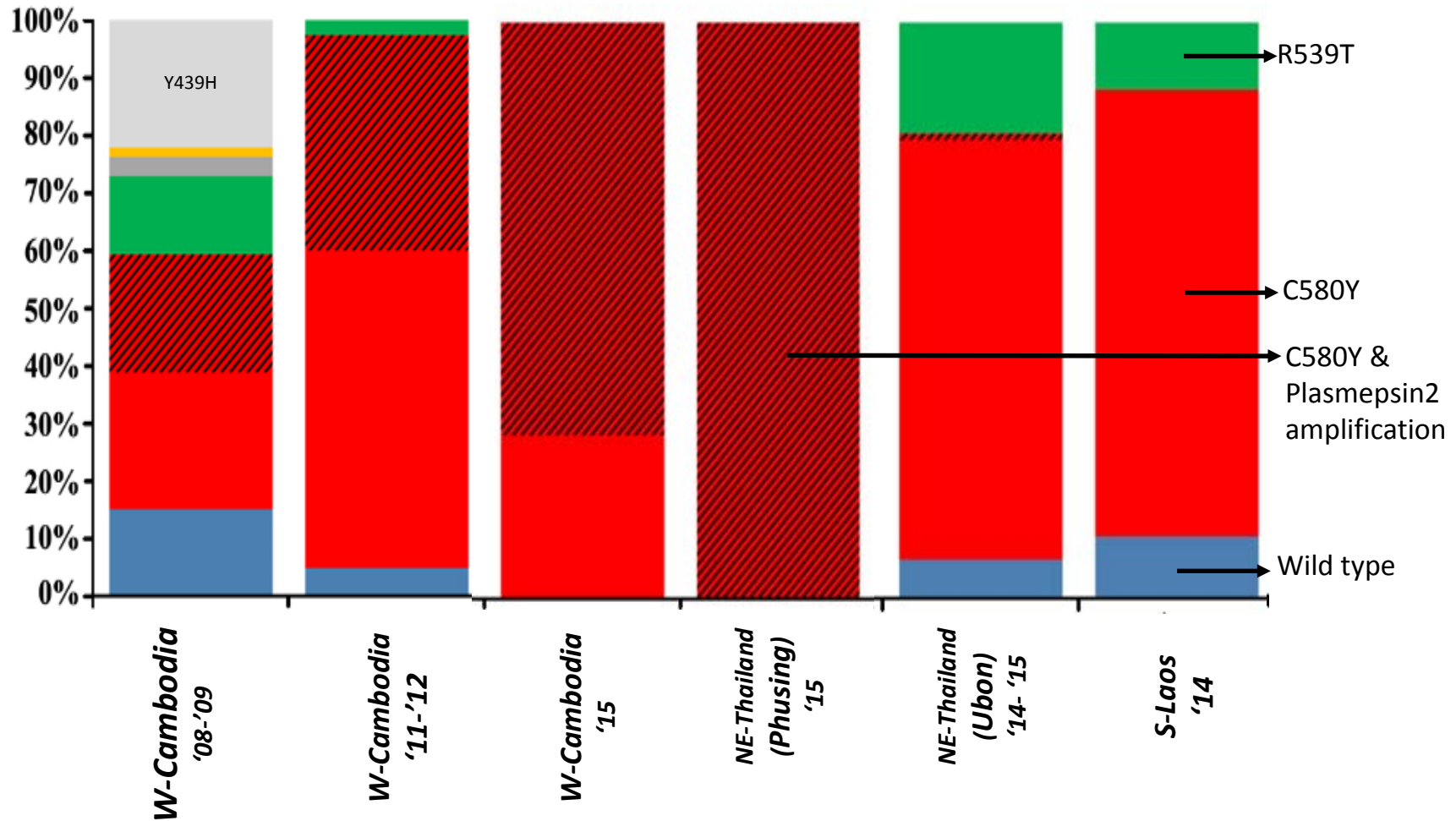
# C580Y “takes over” on the Thailand-Myanmar border



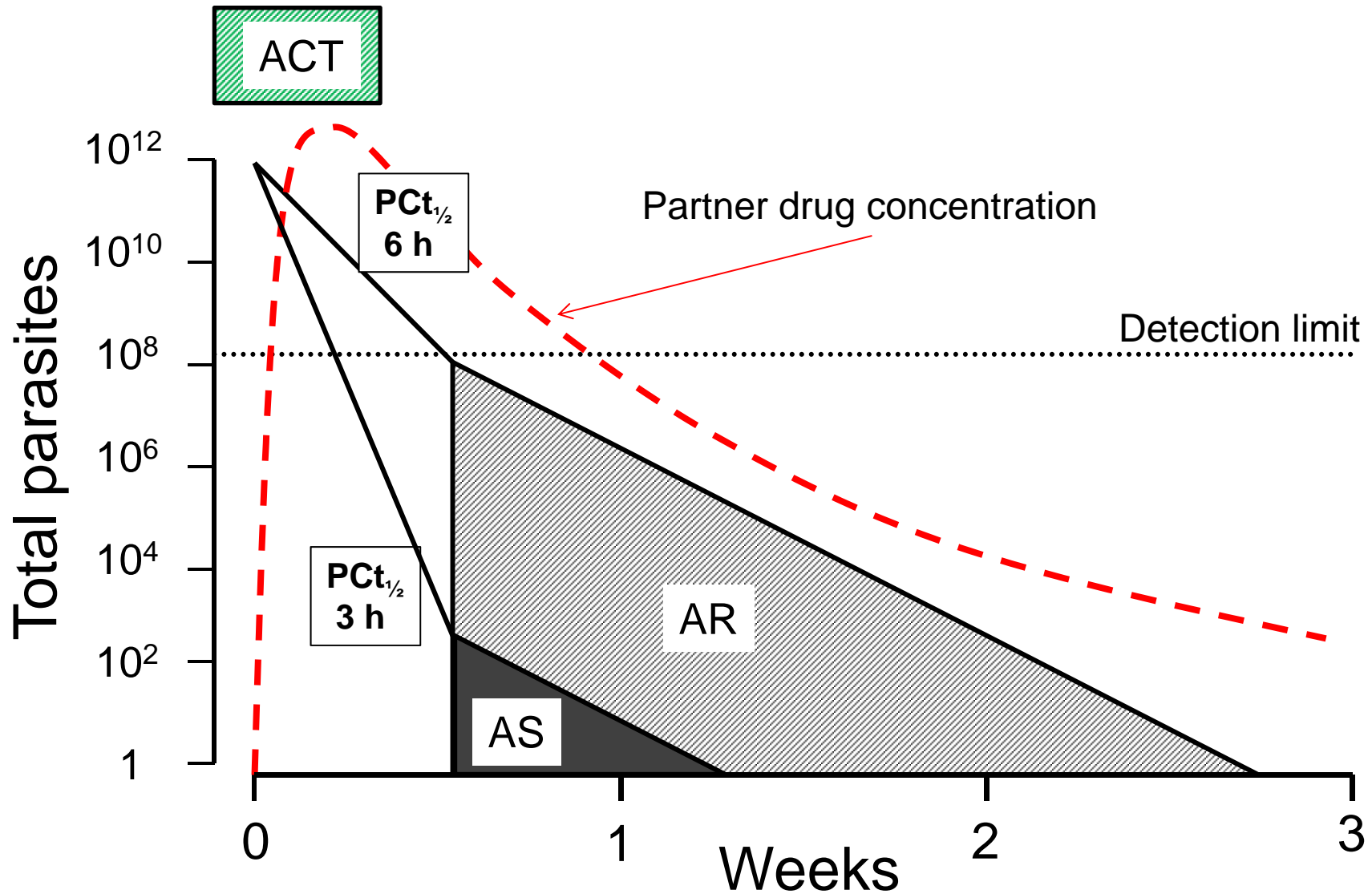
- First *Pfkelch* mutations in 2003
- 90% by 2014
- >75 mutations seen SE Asia
- **C580Y** had taken over  
(but was later eliminated by the Malaria Elimination Task Force)



# C580Y also “takes over” in Cambodia....



# ACT PK-PD in artemisinin resistance



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# Artemisinin resistance: a prelude to ACT failure

## Cambodia

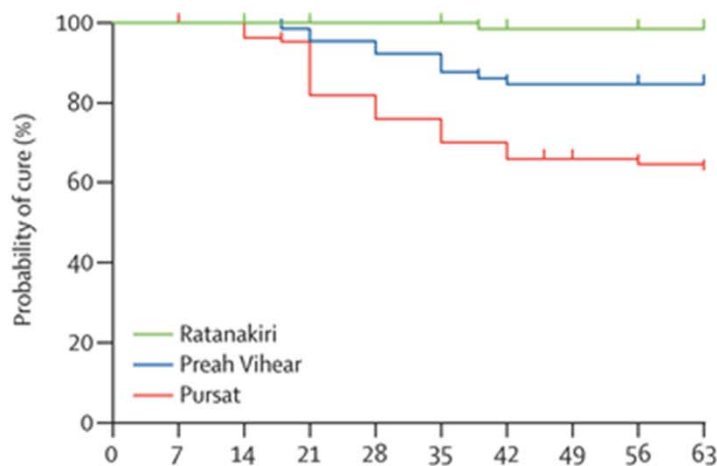
2012-2013

2012-2014



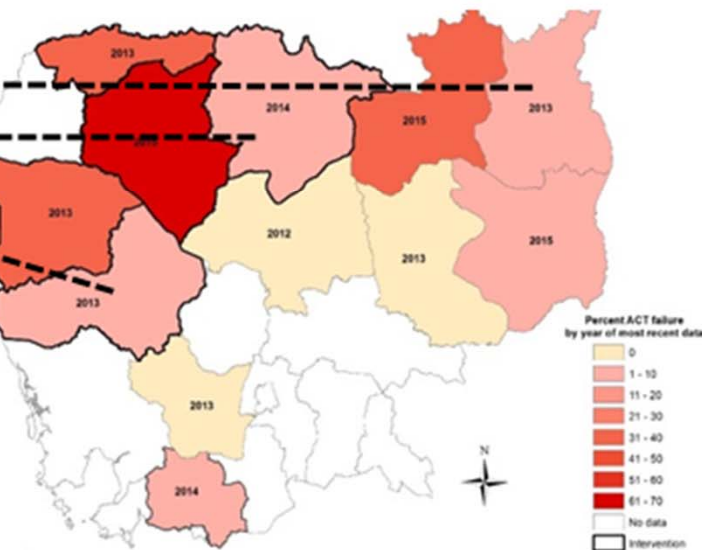
DHA-piperaquine efficacy

DHA-piperaquine 42-day failures



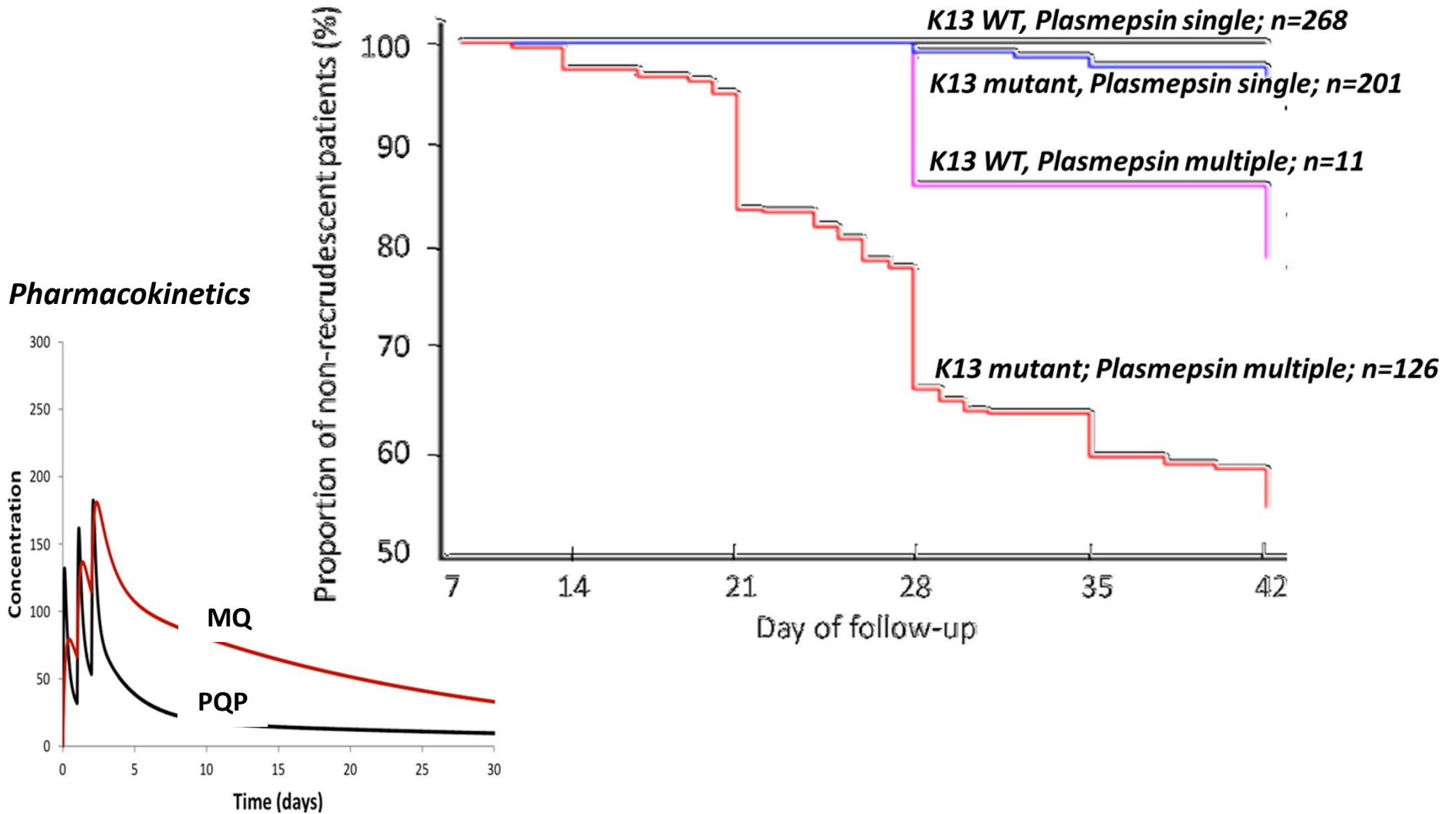
Number at risk

	0	7	14	21	28	35	42	49	56	63
Ratanakiri	66	66	66	65	65	64	62	62	61	60
Preah Vihear	65	65	65	64	62	60	56	56	55	54
Pursat	110	110	106	100	83	75	67	57	53	48



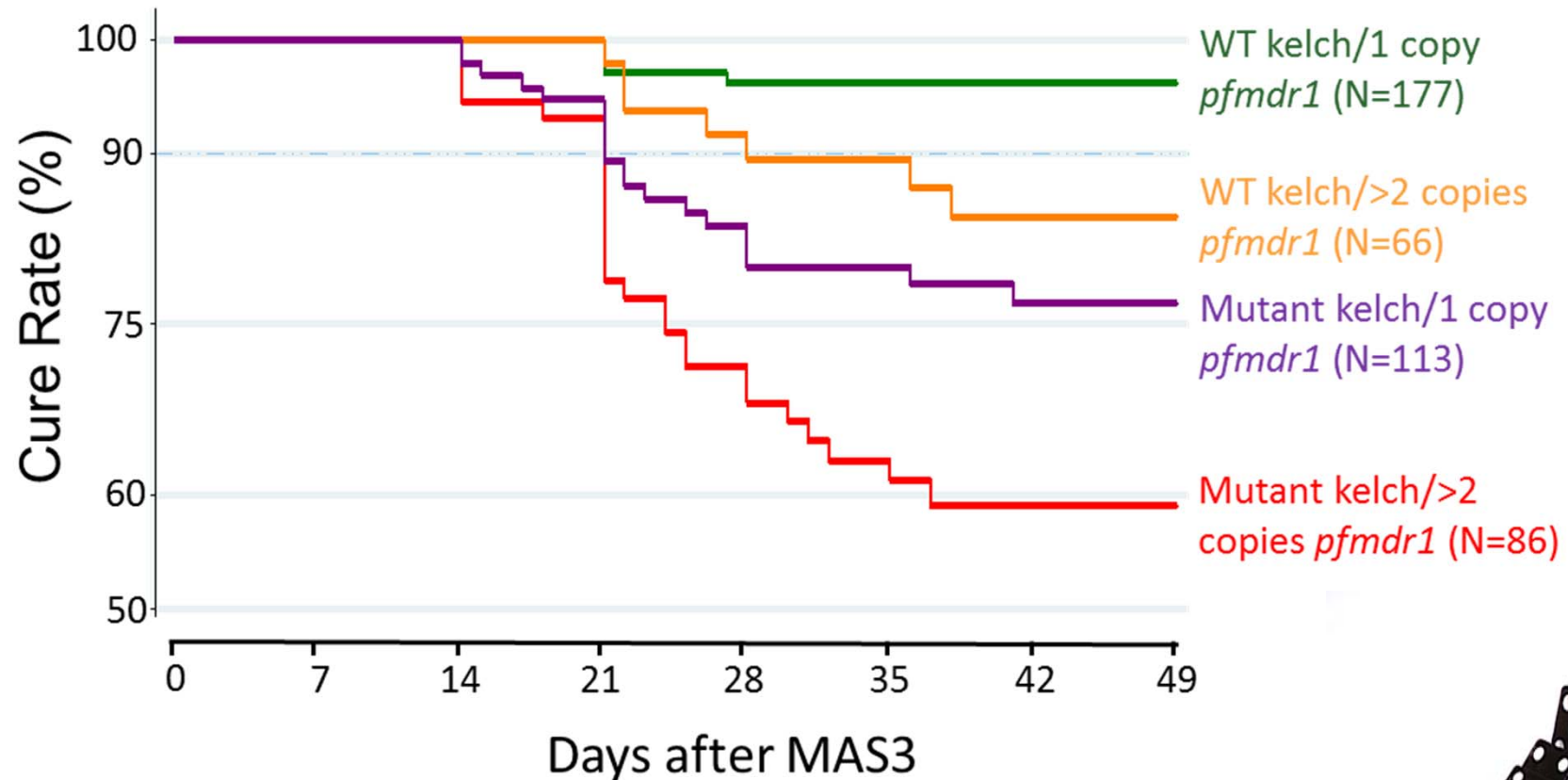
# Artemisinin resistance and ACT treatment failure

## Cambodia



# Artemisinin and mefloquine resistance and ACT failure

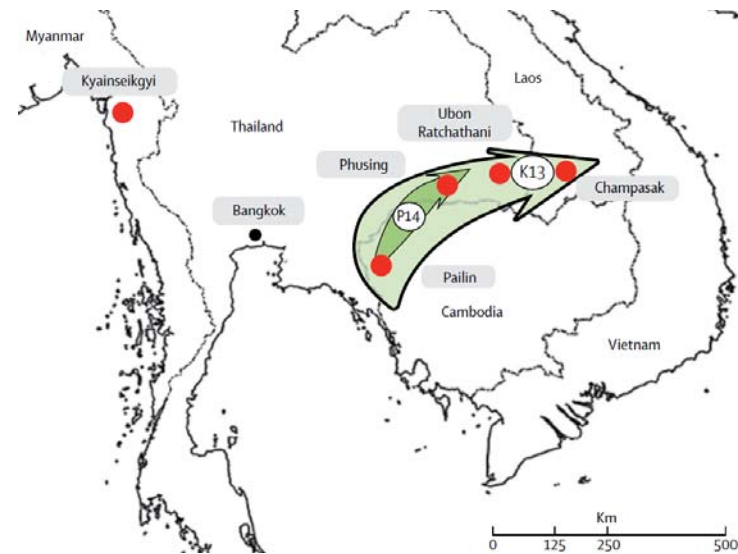
## Thailand-Myanmar border



# PfKelch C580Y takes over.... and spreads

The spread of artemisinin-resistant *Plasmodium falciparum* in the Greater Mekong Subregion: a molecular epidemiology observational study

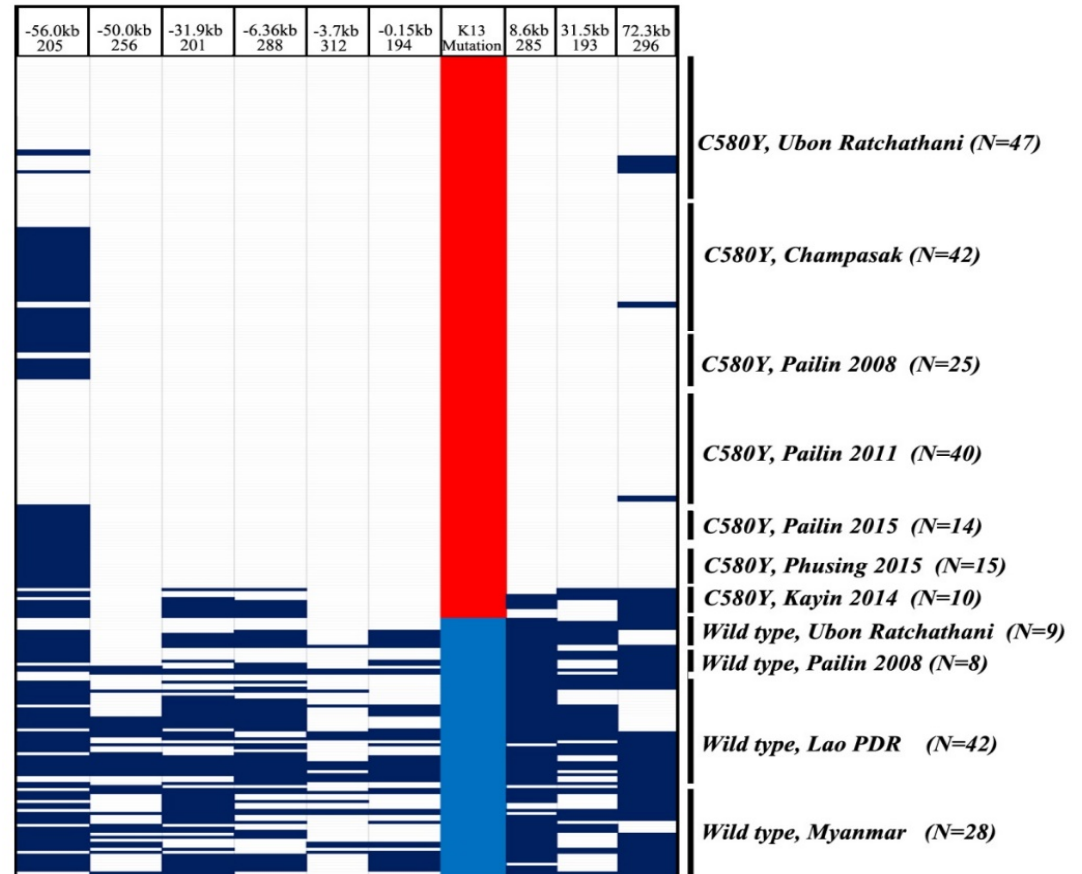
Mallika Imwong, Kanokon Suwannasin, Chanon Kunasol, Kreepol Sutawong, Mayfong Mayxay, Huy Rekol, Frank M Smithuis, Tin Maung Hlaing, Kyaw M Tun, Rob W van der Pluijm, Rupam Tripura, Olivo Miotto, Didier Menard, Mehul Dhorda, Nicholas P J Day, Nicholas J White, Arjen M Dondorp



Genetic markers associated with dihydroartemisinin-piperazine failure in *Plasmodium falciparum* malaria in Cambodia: a genotype-phenotype association study

Roberto Amato, Pharath Lim, Olivo Miotto, Chanaki Amaratunga, Dalin Dek, Richard D Pearson, Jacob Almagro-Garcia, Aaron T Neal, Sokunthea Sreng, Seila Suon, Eleanor Drury, Dushyanth Jyothi, Jim Stalker, Dominic P Kwiatkowski, Rick M Fairhurst

-50 to +31.5kb



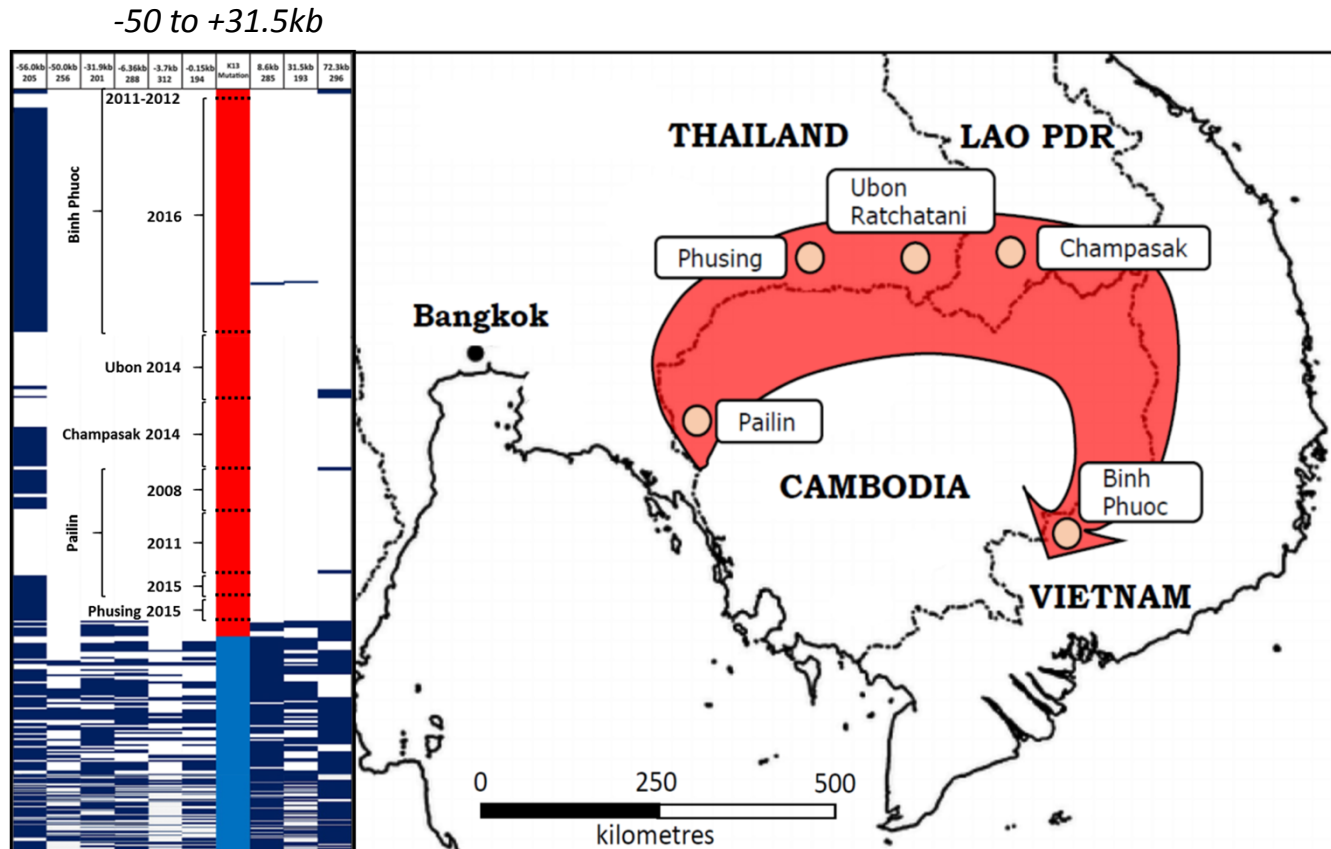
(picking up plasmepsin2/3 amplification)

A single lineage



# *Pf*Kelch C580Y takes over..... and spreads all across the GMS

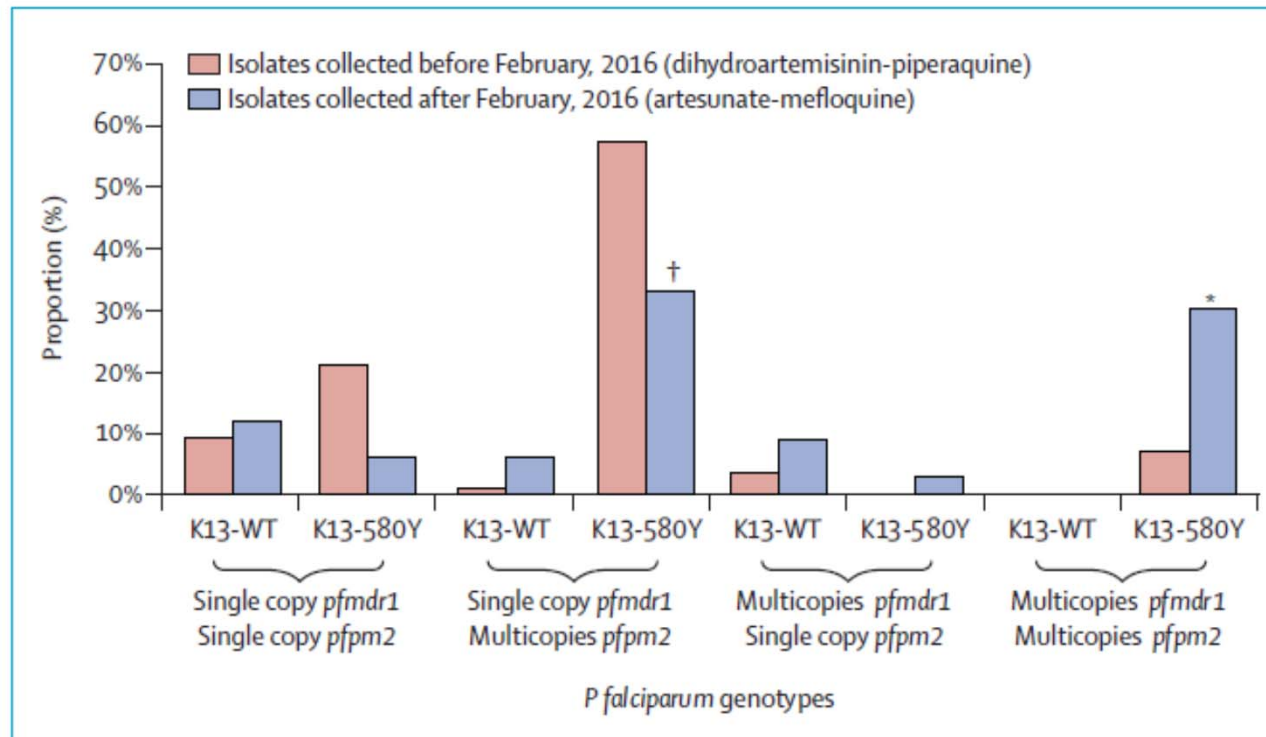
A single multi-drug resistance lineage has now spread across *four* countries



# The “triple” mutant

Emergence of  
*Plasmodium falciparum*  
triple mutant in  
Cambodia

Gabriele Rossi, Martin De Smet,  
Nimol Khim, \*Jean-Marie Kindermans,  
Didier Menard



Lancet ID December 2017

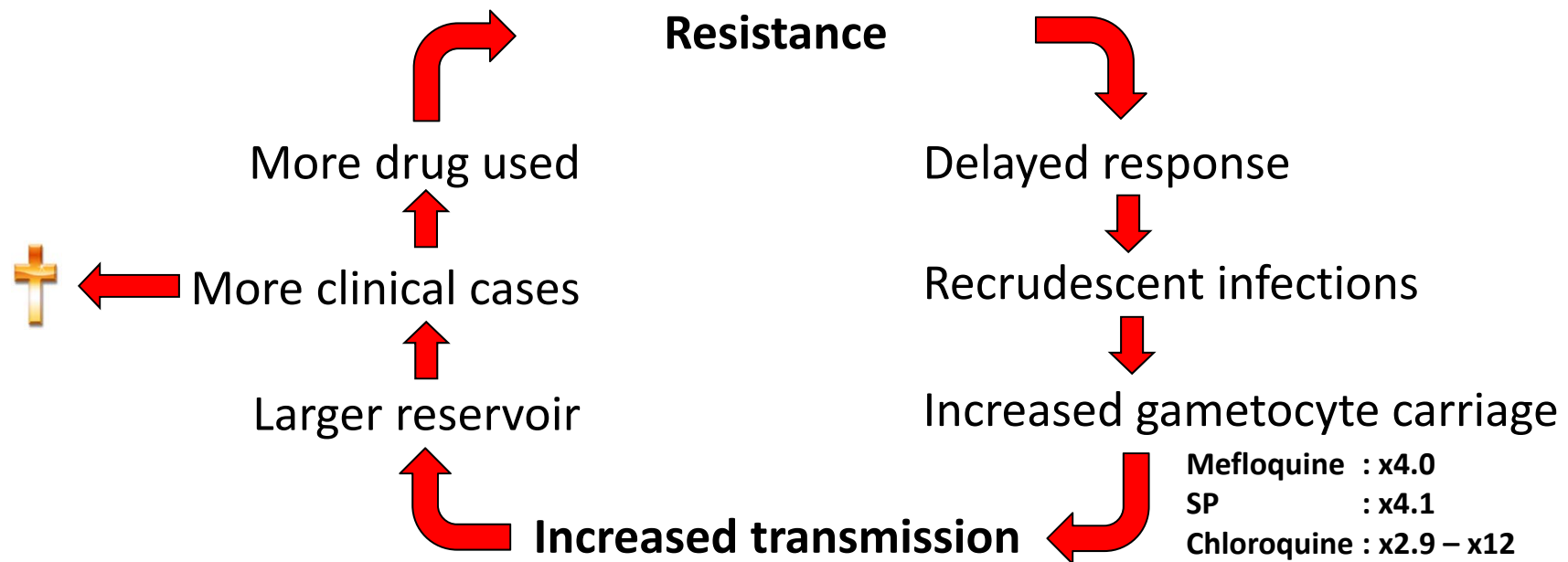


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# ACT failure $\Rightarrow$ $\uparrow$ transmission of drug resistance



*Drakely et al. 2004;  
Barnes & White 2005*



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*Price et al. 1996;  
Bousema et al 2003*

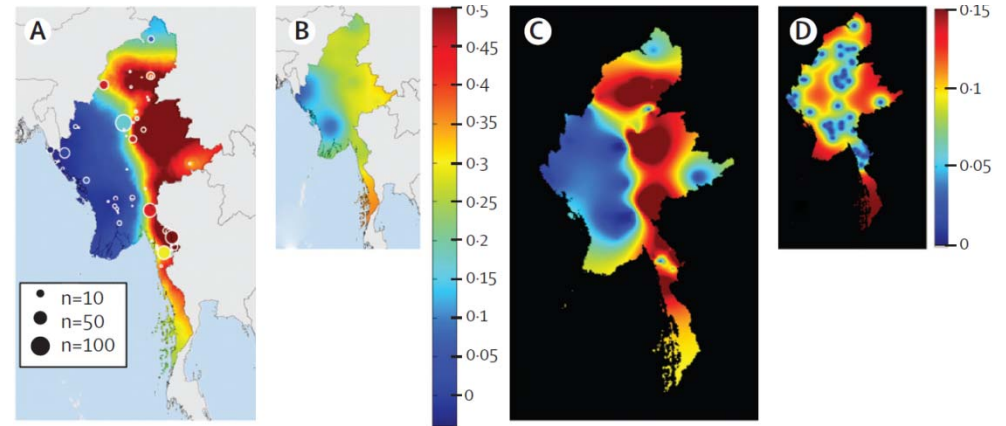
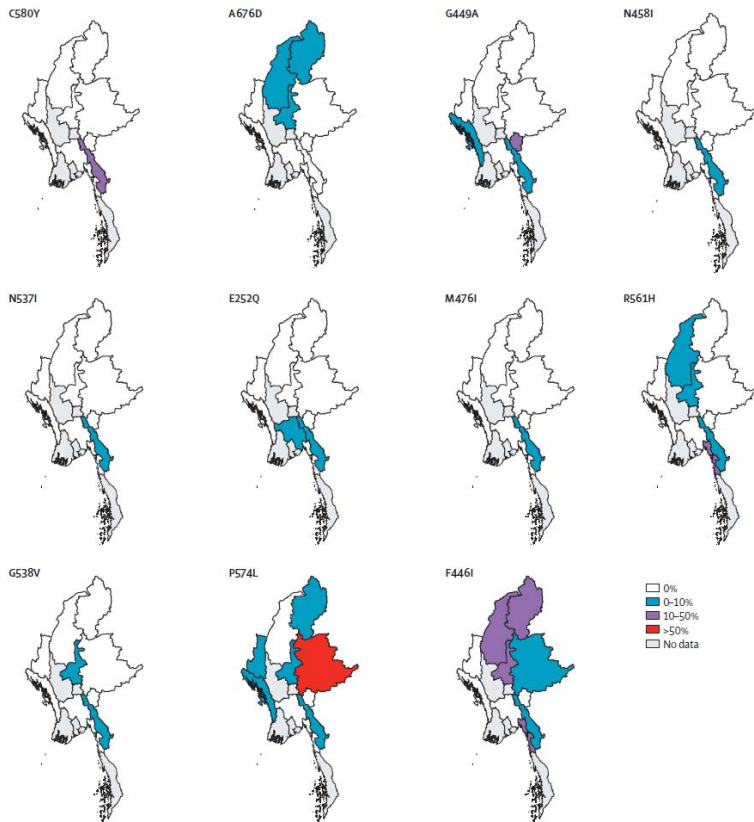
# Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker

Kyaw M Tun, Mallika Imwong, Khin M Lwin, Aye A Win, Tin M Hlaing, Thaung Hlaing, Khin Lin, Myat P Kyaw, Katherine Plewes, M Abul Faiz, Mehul Dhorda, Phaik Yeong Cheah, Sasithon Pukrittayakamee, Elizabeth A Ashley, Tim J C Anderson, Shalini Nair, Marina McDew-White, Jennifer A Flegg, Eric P M Grist, Philippe Guerin, Richard J Maude, Frank Smithuis, Arjen M Dondorp, Nicholas P J Day, François Nosten, Nicholas J White, Charles J Woodrow

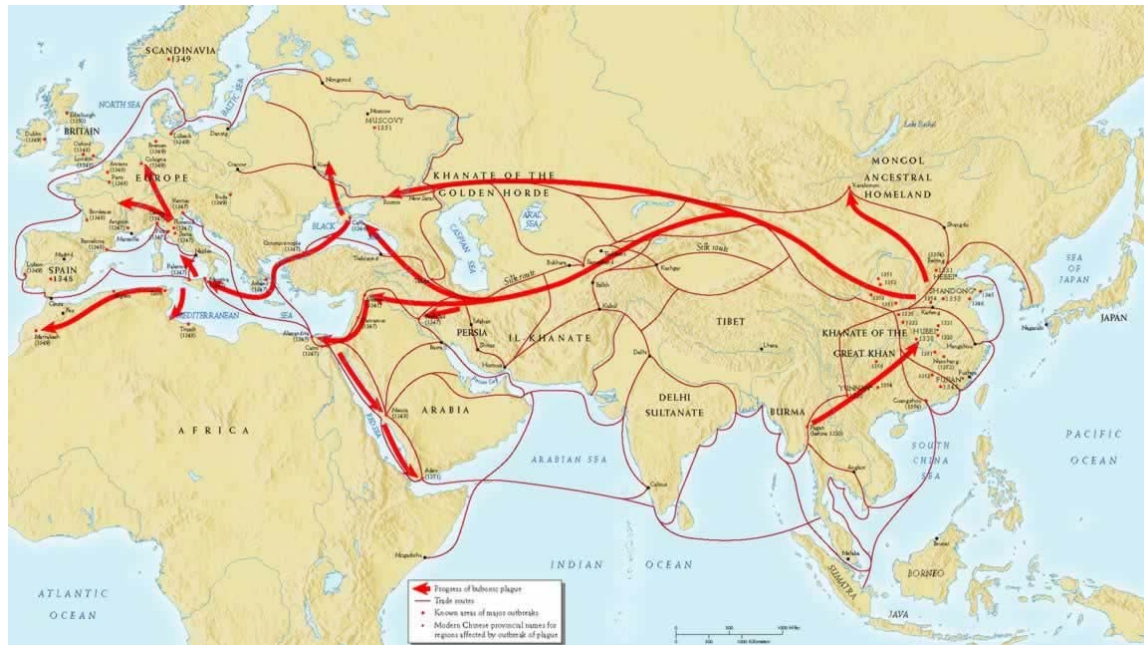
Lancet Infect Dis 2015;  
15: 415–21

Very close to India

November 2017: Now undoubtedly in NE India



# The Black Death

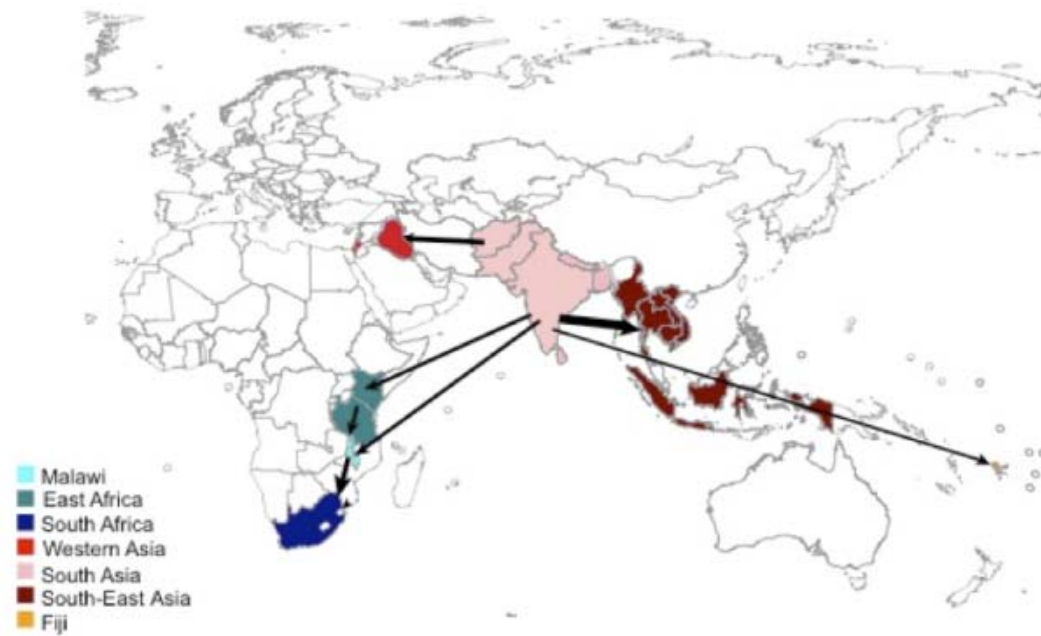


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# *S. Typhi* H58

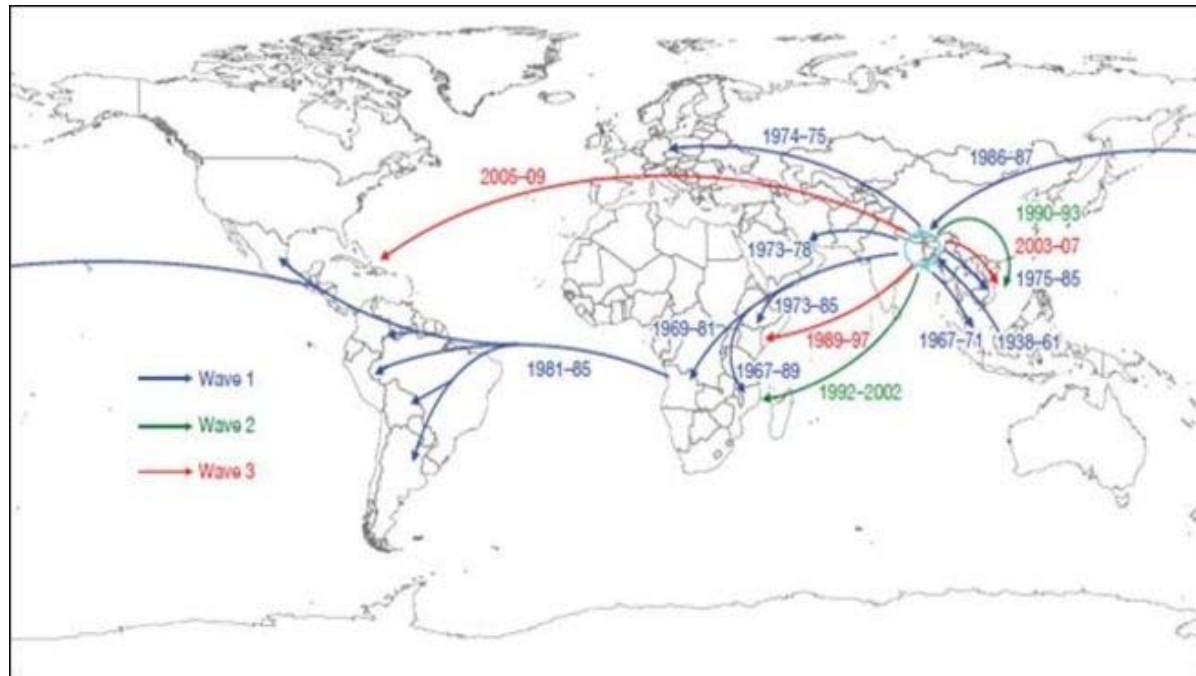


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# Cholera



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# NDM1-beta lactamase

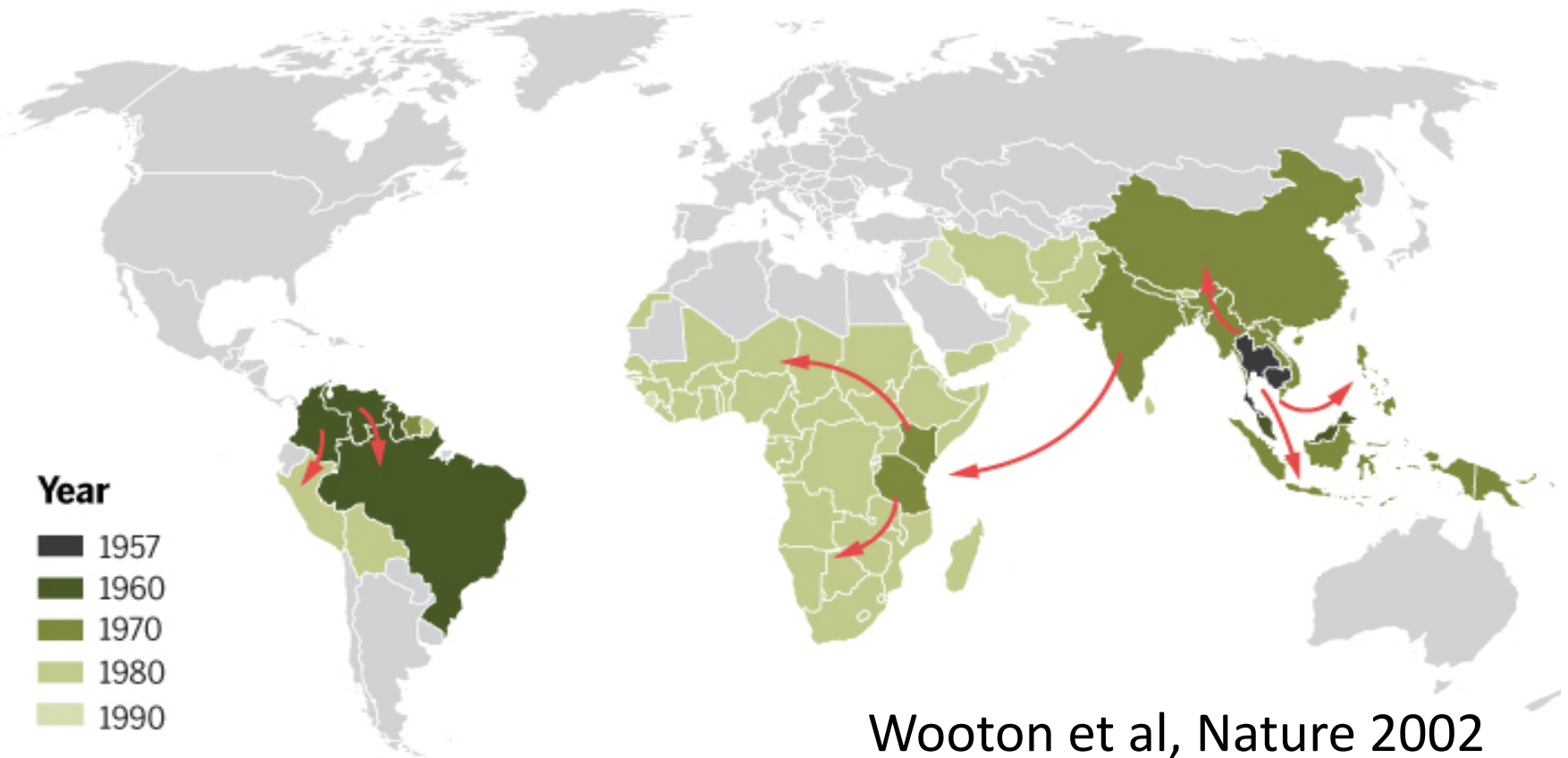


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# Chloroquine resistance



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# Spread of resistance: chloroquine and pyrimethamine

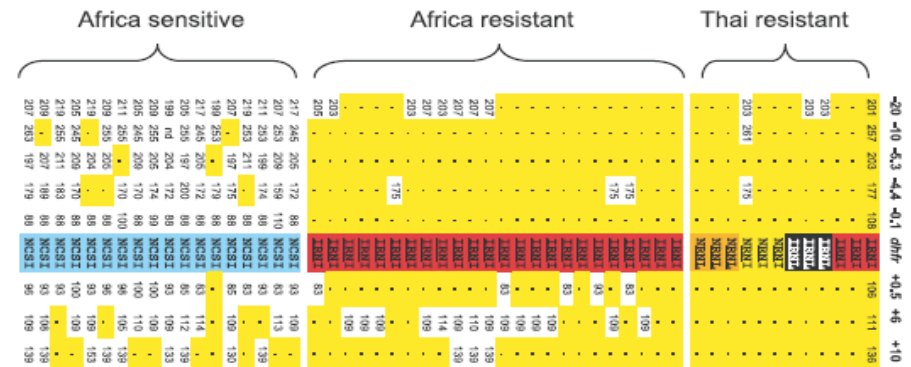
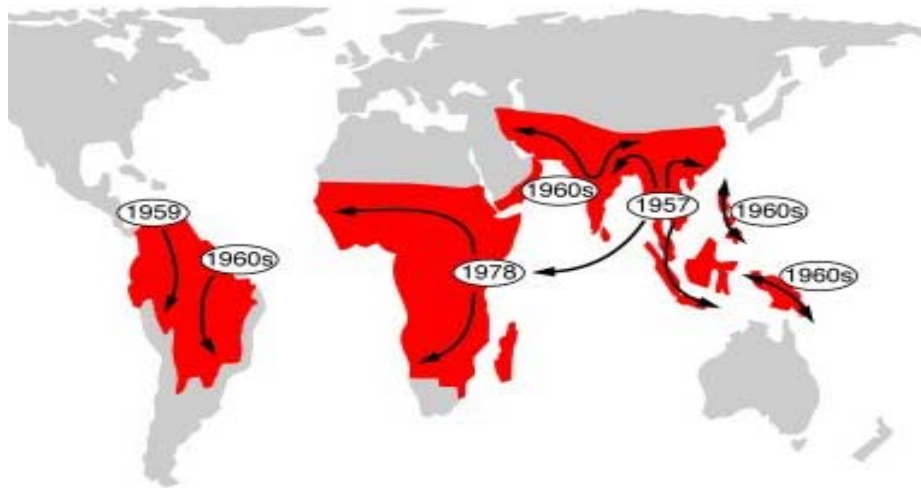


Fig. 1. *dhfr* alleles and flanking microsatellites of parasites from Africa and Thailand. The figure comprises data from 12 Thai parasites with two to four resistance mutations, 24 African parasites with triple-mutant alleles, and 18 African parasites with sensitive *dhfr* alleles. The four-letter codes describe amino acids present at positions 51, 59, 108, and 164 in the predicted *dhfr* protein (10). Amino acids conferring resistance are underlined, and *dhfr* alleles are shaded yellow, orange, red, and black in order of increasing resistance. Sensitive alleles are shaded turquoise. Allele lengths are shown for eight microsatellites positioned at -0.1, -4.4, -5.3, -10, and -20 kb upstream and +0.5, +6, and +10 kb downstream of *dhfr*. Dots and yellow shading indicate identical allele size to the predominant resistant haplotype (shown at right).



Dondorp et al  
Nat Rev Microbiol. 2010



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Roper et al  
Science 2004



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**Radical measures are needed**





WHO meeting,  
"Getting to Zero by 2020"  
16 - 17 March 2017  
Geneva, Switzerland

# WHO seizes the initiative.....

Global **Malaria** Programme



## Artemisinin and artemisinin-based combination therapy resistance

APRIL 2017

STATUS REPORT



### Conclusion

Despite the delayed response to artemisinin in some areas of the GMS, ACTs remain the most effective treatment for uncomplicated falciparum malaria. Most patients with delayed parasite clearance are cured, as long as the partner drug remains effective. Routine monitoring must continue in order to ensure that the recommended ACTs are effective, that timely changes to national treatment policies can be implemented, and that artemisinin resistance can be detected early. Assessment of K13 propeller region mutants will greatly facilitate the tracking of artemisinin resistance as it emerges. In the context of multidrug resistance including ACT resistance in the GMS, elimination of falciparum malaria has become a high priority. The role played by artemisinin resistance in the development or selection of partner drug resistance needs to be further evaluated.

# Accelerating towards elimination

**ELIMINATING MALARIA**  
IN THE GREATER MEKONG SUBREGION

**UNITED**  
TO END A DEADLY DISEASE



## How WHO is helping countries accelerate towards malaria elimination

For more than 60 years, WHO has provided guidance and technical support to all countries with ongoing malaria transmission. WHO's work in the GMS is supported by technical experts based at six country offices, regional offices in New Delhi and Manila, the MME hub in Phnom Penh, and WHO's Geneva headquarters.

WHO is committed to helping countries achieve their malaria goals through:

- setting and disseminating global guidance and policies on malaria control and elimination;
- supporting countries as they adapt, adopt and implement WHO global norms and standards for malaria control and elimination;
- assisting countries as they formulate national malaria strategic plans;
- helping countries develop robust malaria surveillance systems;
- responding to requests from countries to address biological threats, operational emergencies and bottleneck issues.



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Artemisinin tolerance rather than resistance as it affects only ring stages.

Partner drugs resistance is similarly or even more an important threat than artemisinin tolerance alone:

Artemisinin tolerance has not lead to ACT treatment failure (except in Mae Sot)

No increase of morbidity or mortality in the GMS  
(Overall reduction over the last 10 years is around 50%)

Artemisinin resistance has not driven emergence of piperazine resistance in Cambodia.

Protect the partner drug in particular in Africa. Resistance can be delayed (in contrast to artemisinin tolerance which will emerge whatever we do, due to ACT drug pressure).



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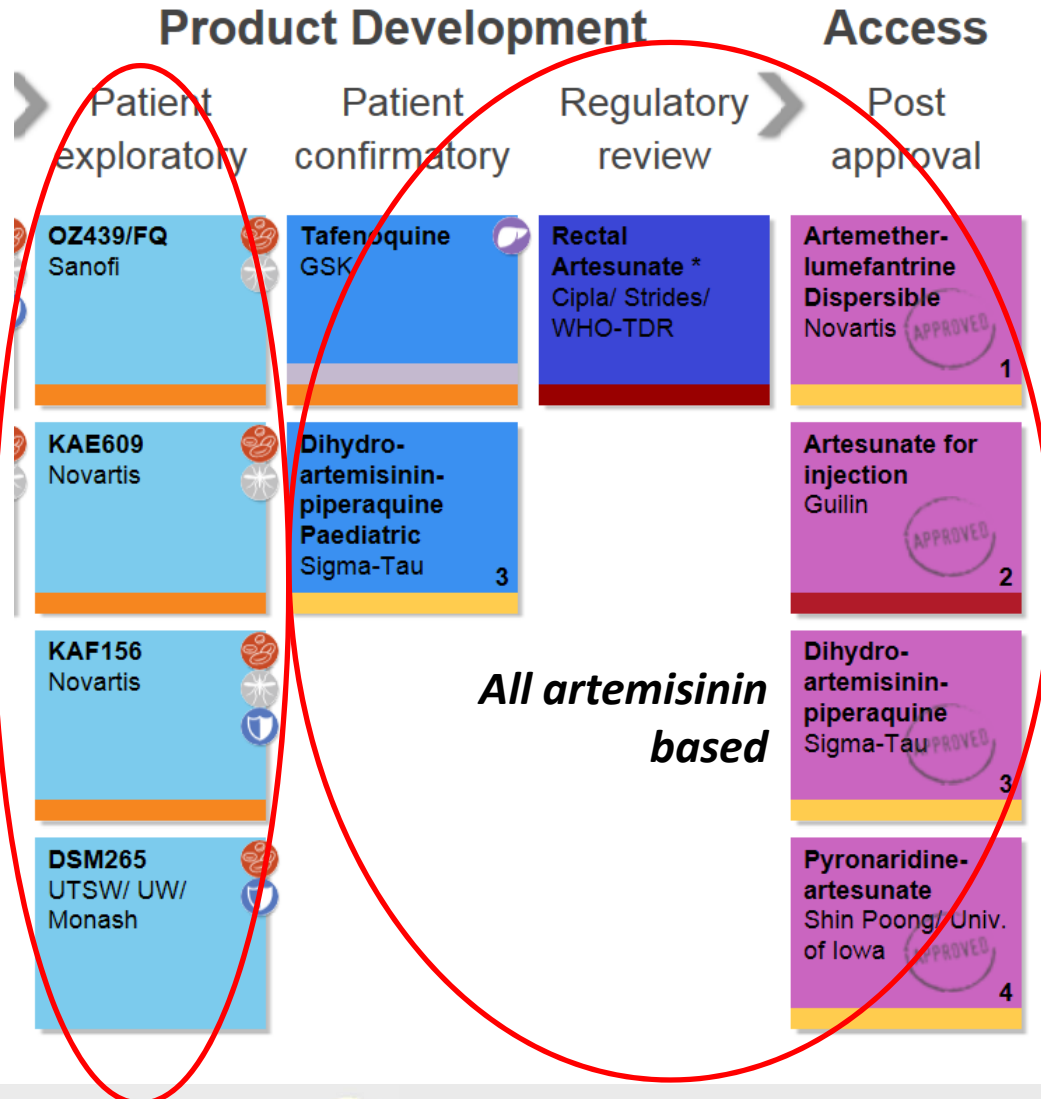


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# Drug development pipeline



**New compounds  
(no artemisinins)**



Source: MMV website



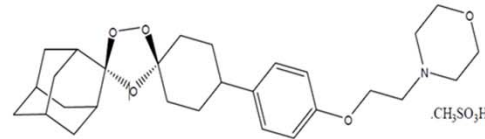
**Mahidol Oxford**



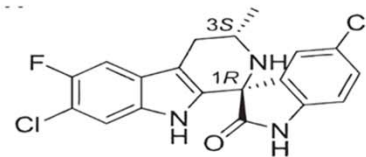
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# New antimalarial drugs: $\geq 5$ years away from registration

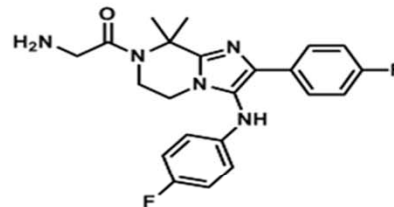
- **Ozonides**  
(OZ 439; Artefenomel)



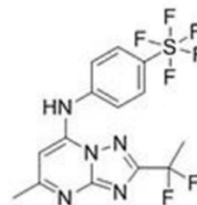
- **Spiroindolones**  
(KAE609; Cipargamin)



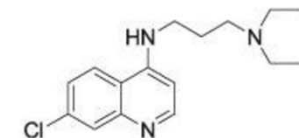
- **Imidazolopiperazine**  
(KAF156)



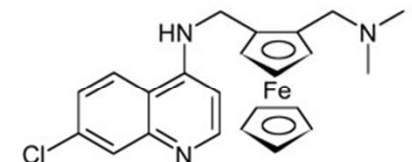
- **DSM265**  
(dihydroorotate dehydrogenase inhibitor)



- **Modified 4-aminoquinolones**  
(AQ13; Ferroquine)



AQ-13



Ferroquine



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## Options with failing ACTs using existing drugs

1<sup>st</sup>. **Triple therapies (TACT): DHA-PQP-MQ; AM-LUM-AQ: *TRAC II***

2<sup>nd</sup>. **5-day regimen of DHA-PQP or AM-LUM**

Needs trialing & reassurance of safety concerns (QTc-prolongation); new problem: PQP resistance.

3<sup>rd</sup>. **Drug rotation of DHA-PQP and MAS3,**

guided by prevalence of PfMDR1 copy-number

4<sup>th</sup>. **Sequential use of two different ACTs (e.g. DHA-PQP and MAS3)**

5<sup>th</sup>. **Artesunate-pyronaridine** efficacy<90%; cross resistance with PQP??

6<sup>th</sup>. **Arterolane-piperaquine**



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