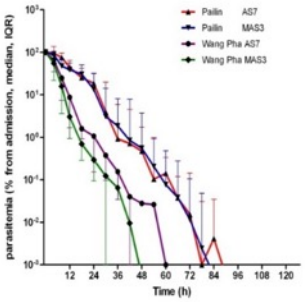
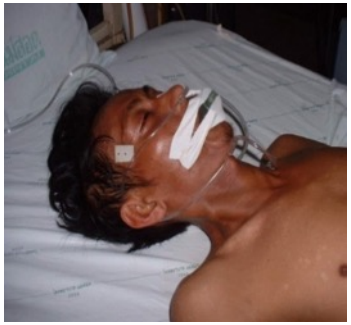
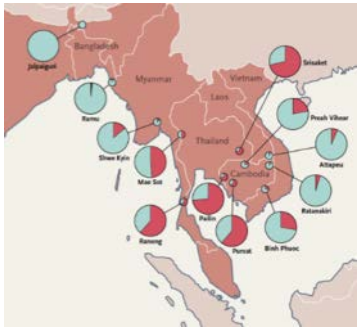
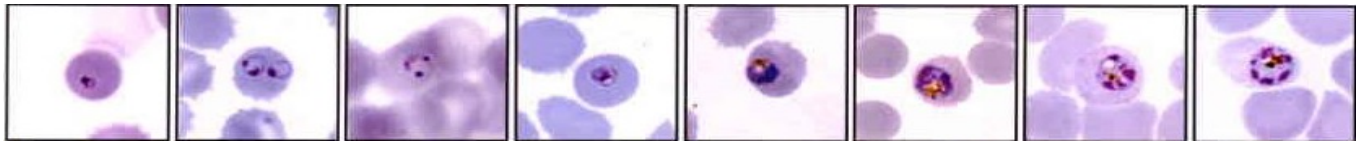
Background on Malaria and Combination Anti-Malarial Drug Therapy









FDA Workshop: Clinical Trial Design Considerations for Malaria Drug Development
30 June 2016

Prof. Arjen M. Dondorp
Mahidol Oxford Tropical Medicine Research Unit

Mahidol Oxford
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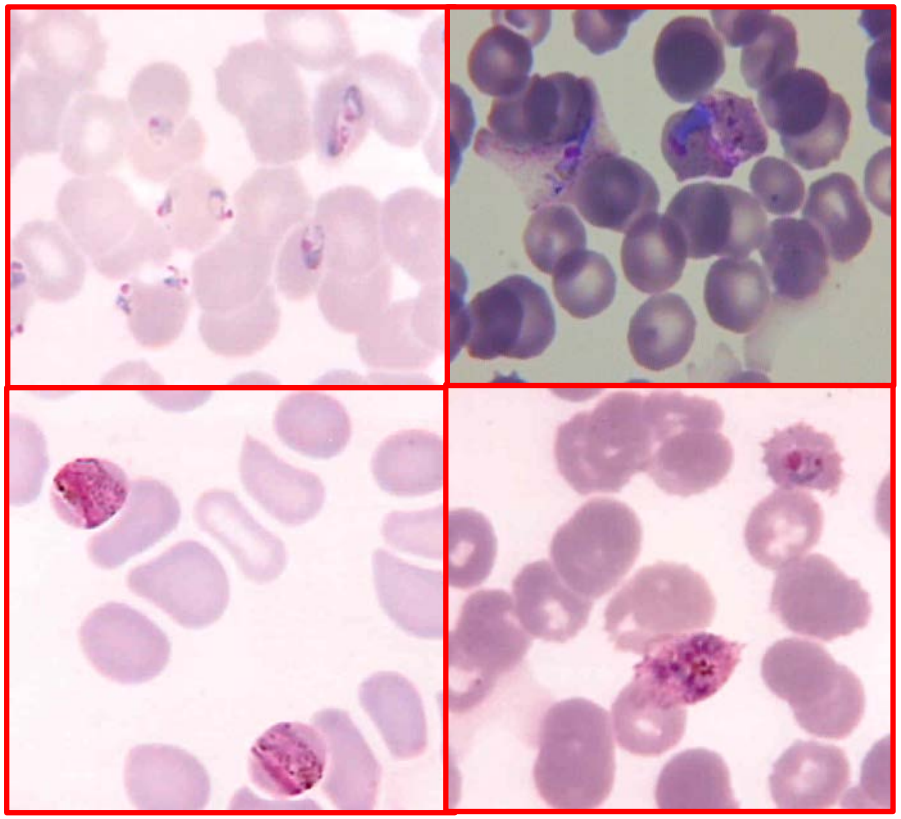
The 5 human *Plasmodium* species

P. falciparum

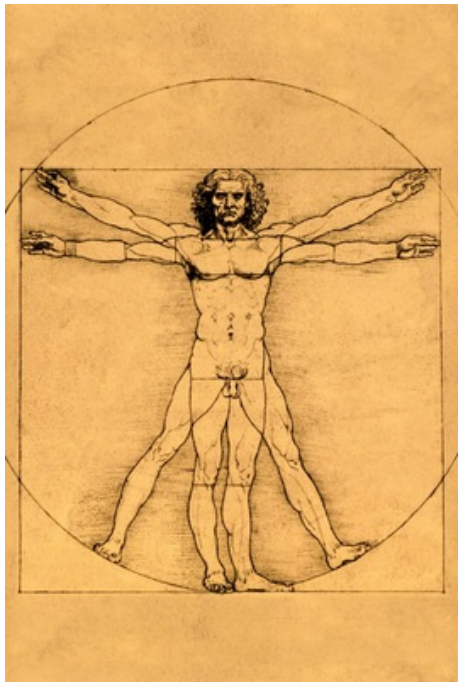
P. vivax



P. malariae

P. ovale

Anopheles

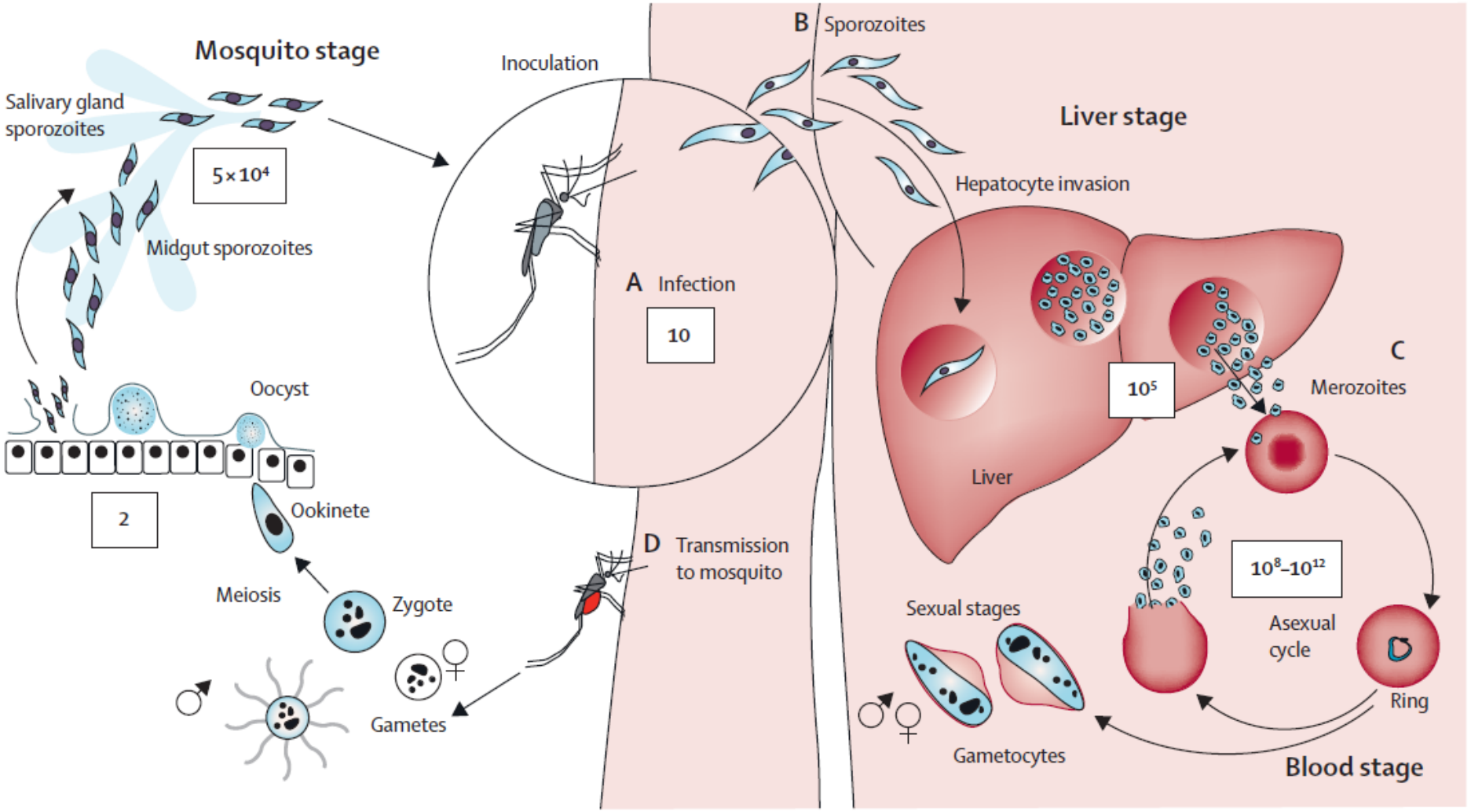


H. sapiens

P. knowlesi

M. fascicularis/ nemestrina

Life-cycle of *Plasmodium*



White et al; Lancet 2014

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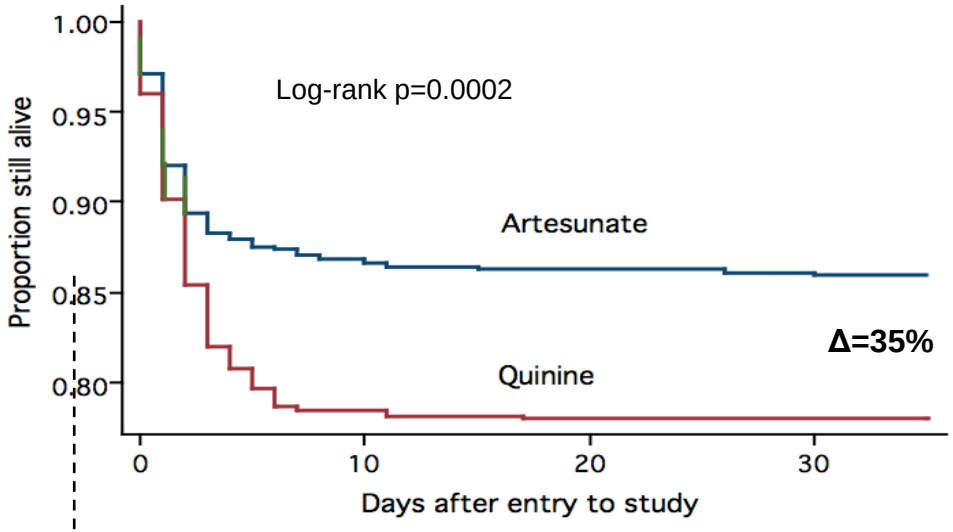
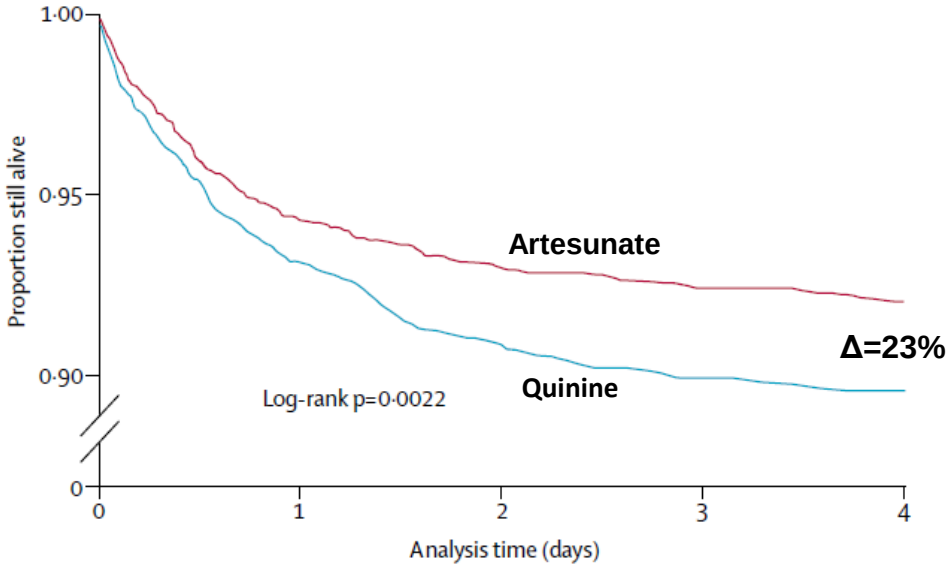
Artemisinins: the best drugs for reducing malaria mortality





SEAQUAMAT

Asia
4 countries
N=1,461
(202 children)

AQUAMAT

Africa
9 countries
N=5,425
(all children)

Dondorp et al. Lancet 2010;
SEAQUAMAT investigators group. Lancet 2005

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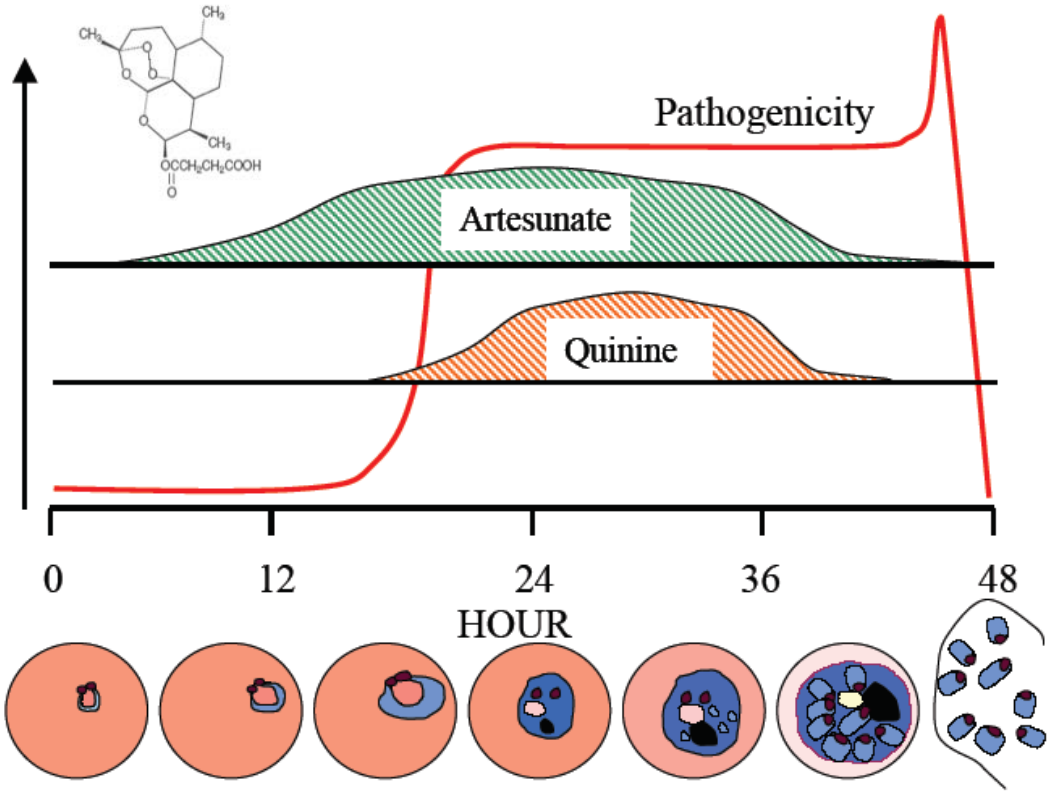
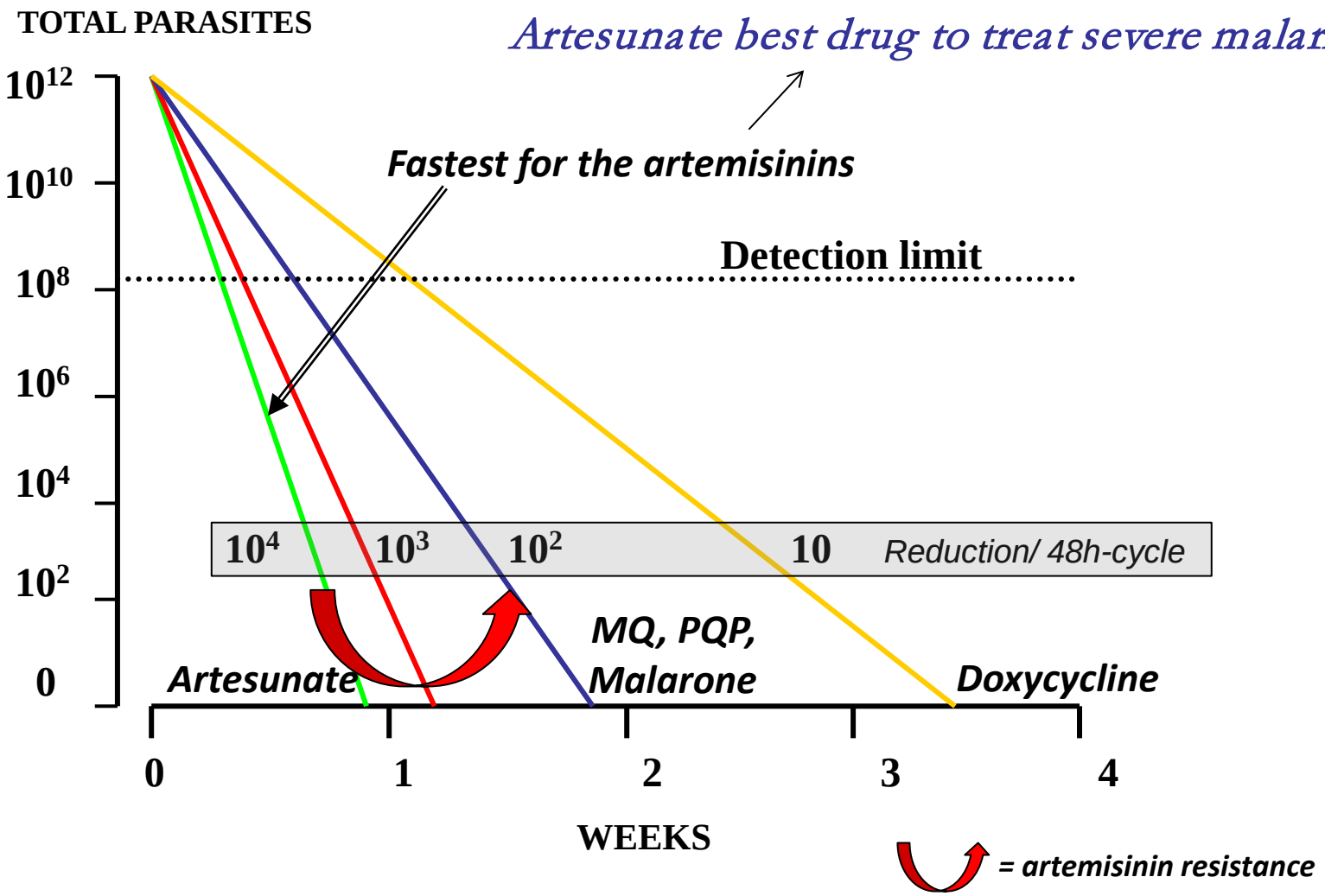
Broader stage specificity explains superiority of artemisins



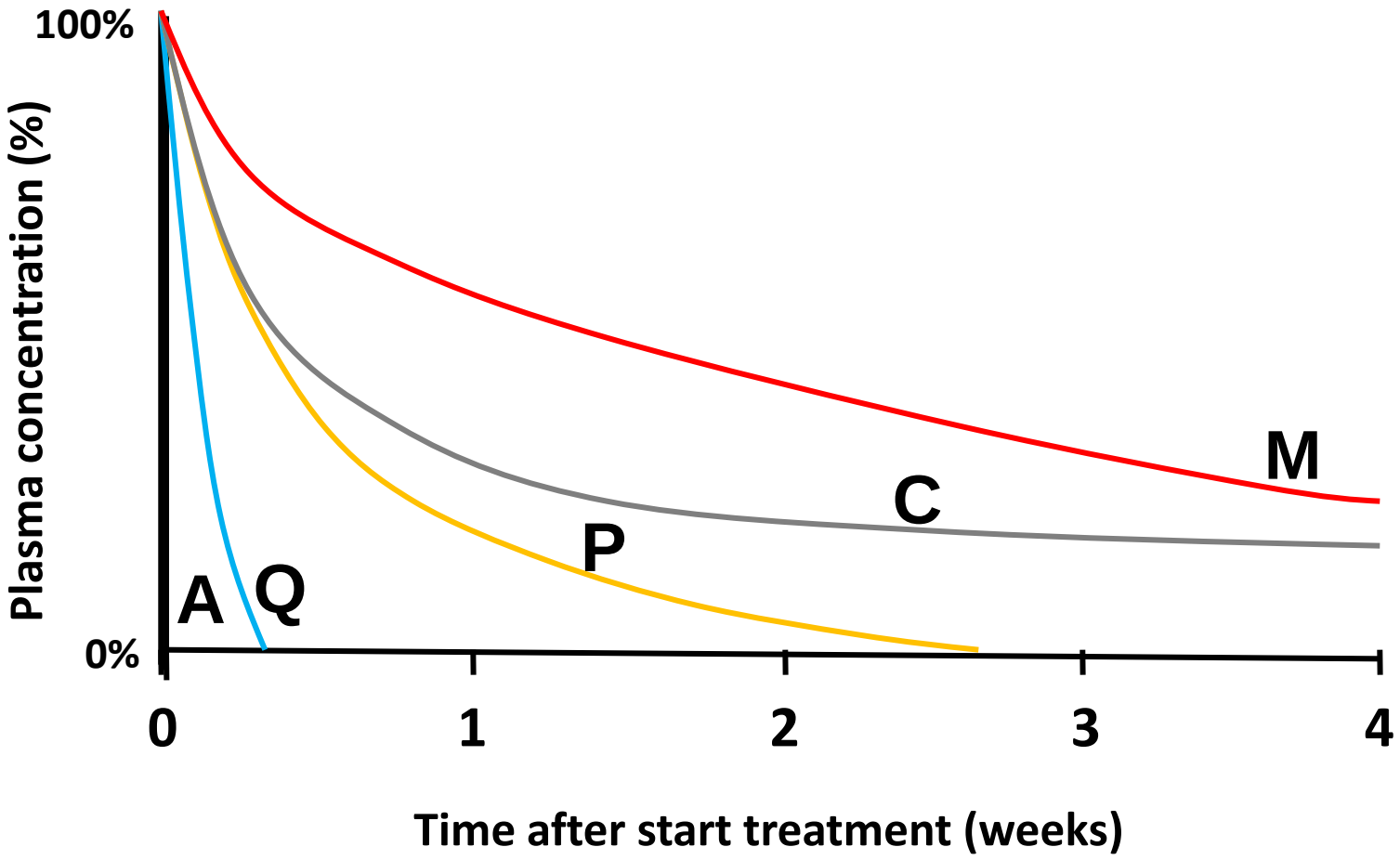
White; Science 2009

Differences in potency



Courtesy NJ White

Differences in pharmacokinetics



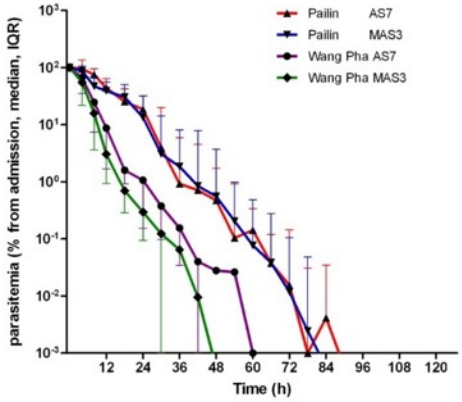
Courtesy NJ White

Artemisinin resistance: a prelude to ACT failure

1. W-Cambodia

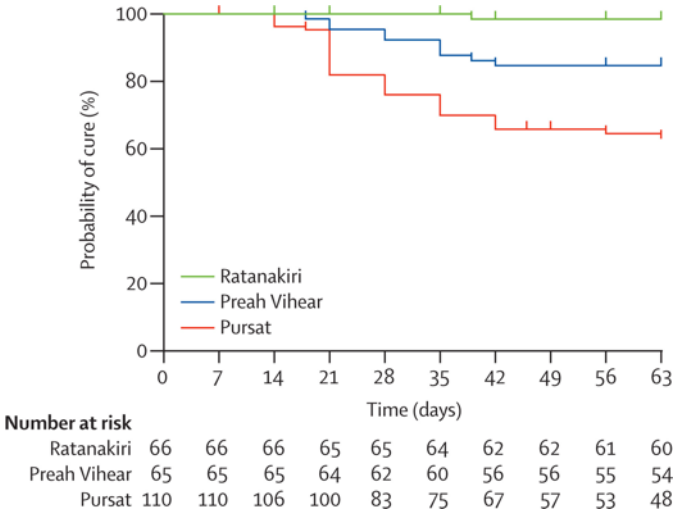
2007-2008

Slow clearance



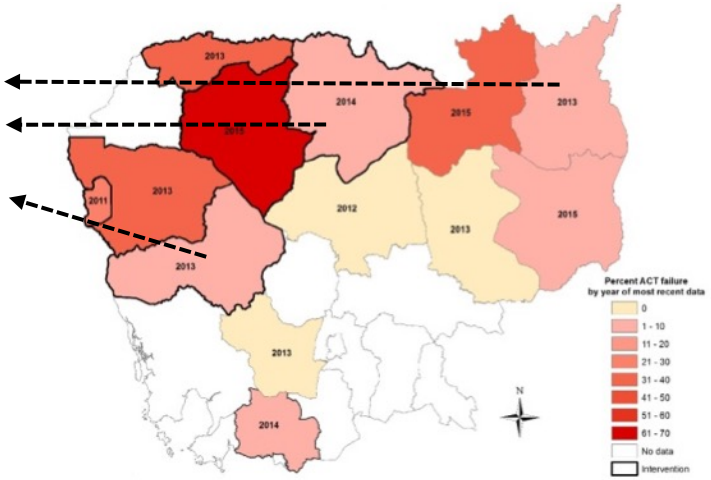
2012-2013

DHA-piperquine efficacy



2012-2014

DHA-piperquine 42-day failures



Source CNM Cambodia/ WHO
Map by Richard Maude

Dondorp et al.
N Eng J Med 2009

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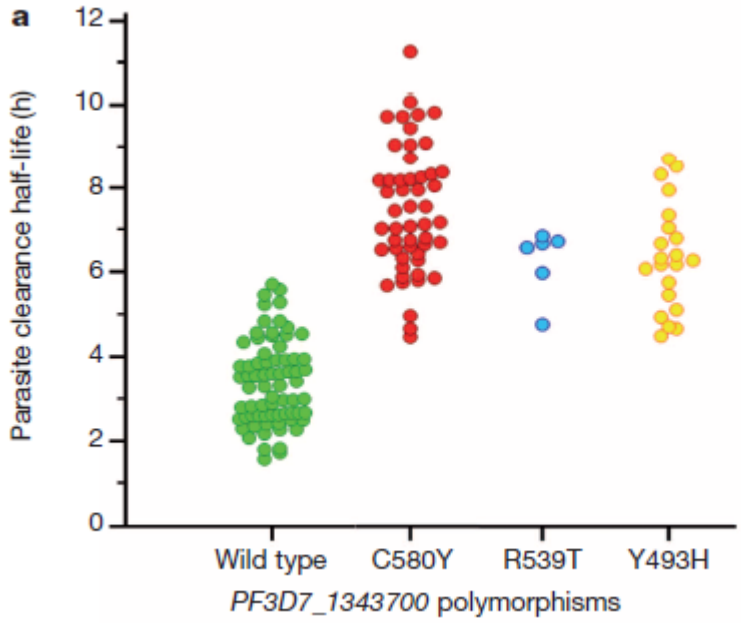
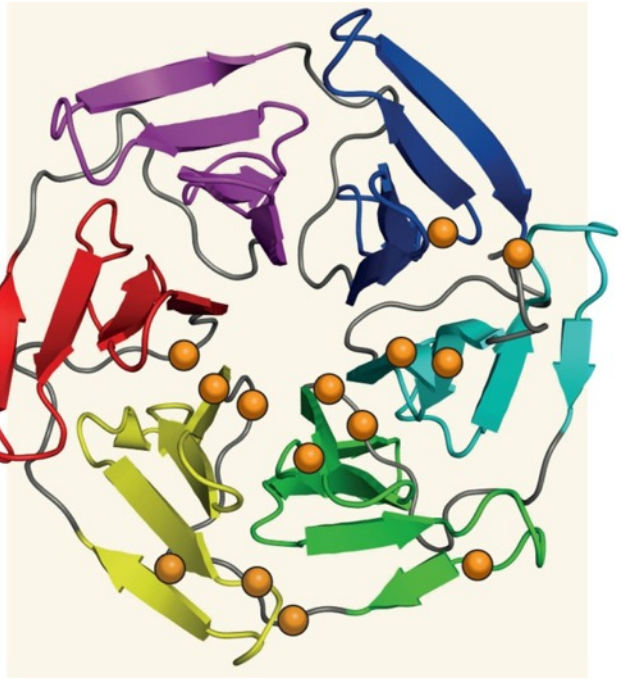
Amaratunga et al.
Lancet Infect Dis 2016

The molecular marker for artemisinin resistance: Kelch 13

K13 mutations in the “propeller region” strongly associates with the slow clearing phenotype

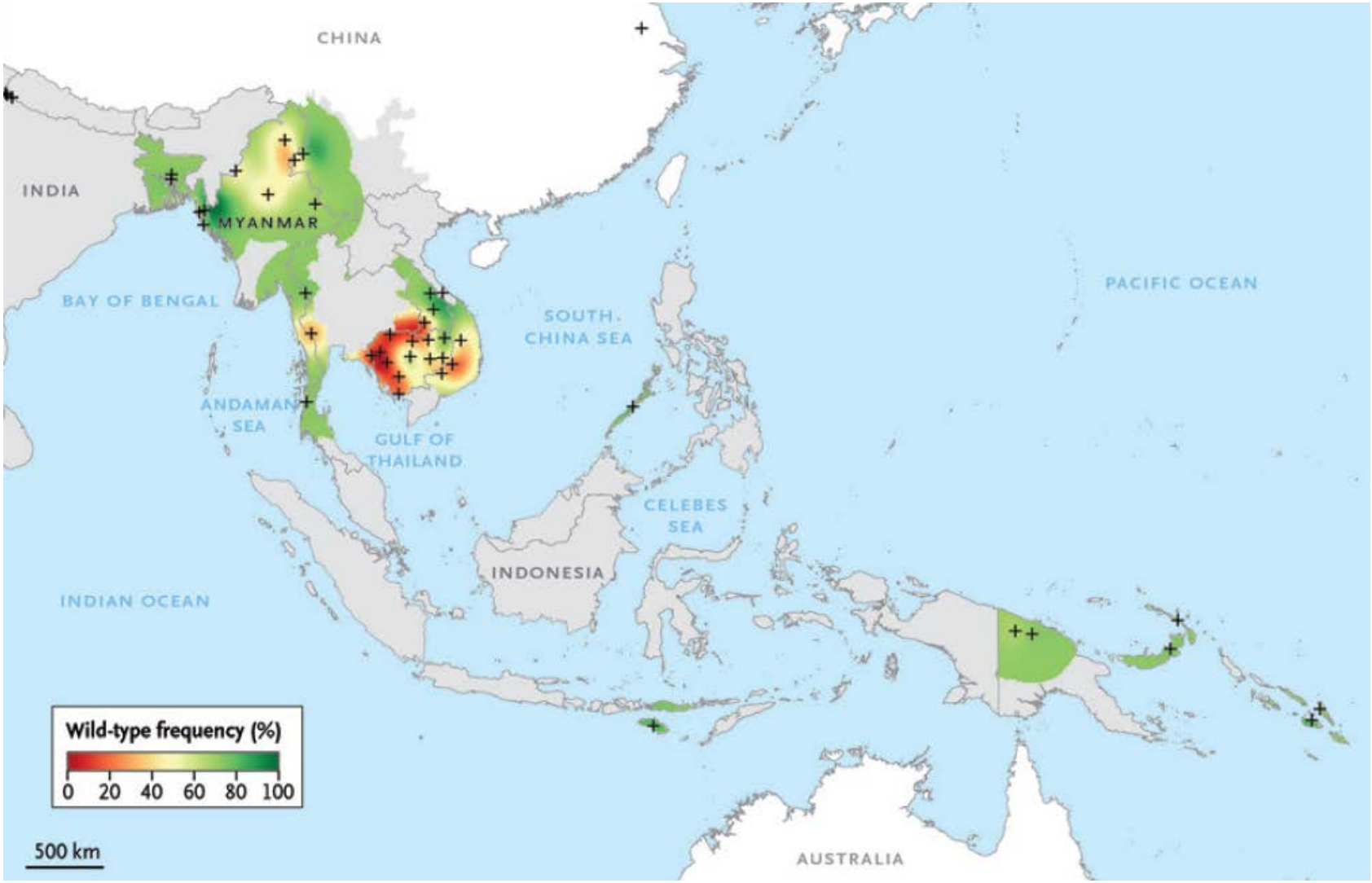




multiple SNPs in the propeller region, but: only 1 mutation per clone seems permitted

Ariey et al. Nature 2013

Regional distribution of Kelch13 Δ propeller 2015



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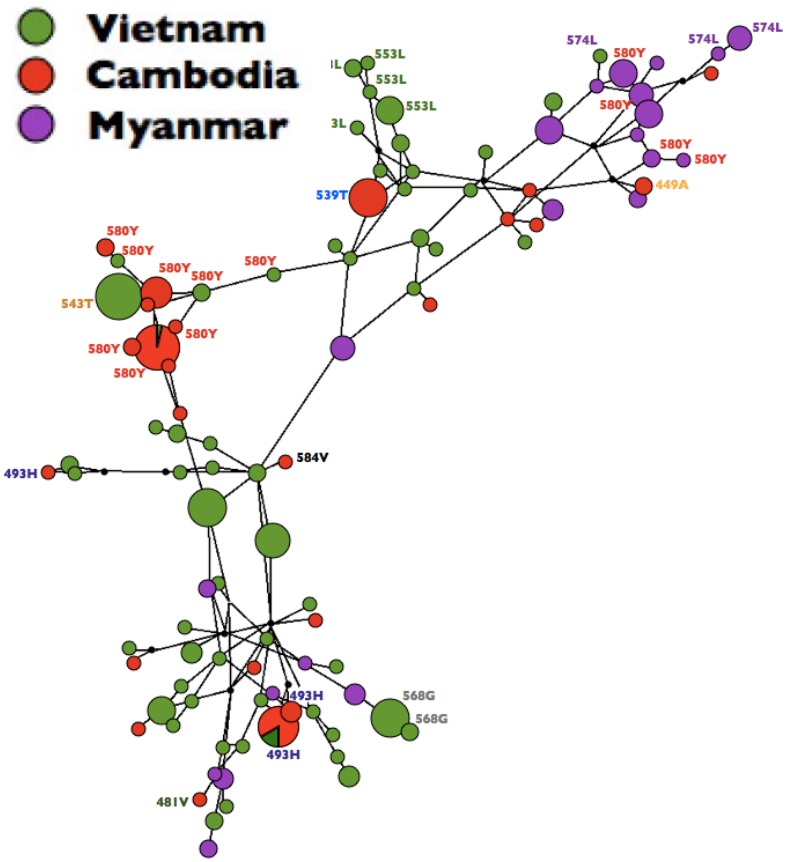
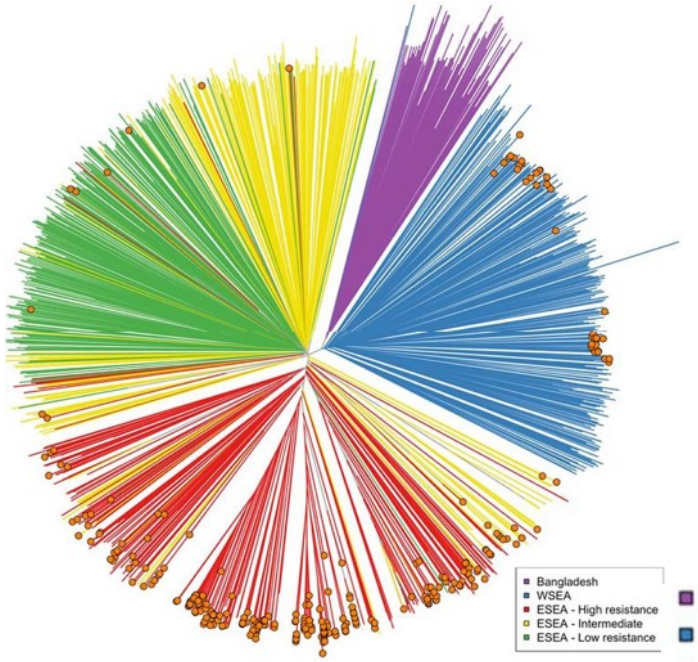
Menard et al.
N Engl J Med 2016

jumping versus popping



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

K580Y mutant found in Myanmar did not spread from Cambodia -it arose independently in Myanmar

Shannon Takala-Harrison et al J Infect Dis 2014

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Miotto et al. Nature Gen 2015

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

Summary

Background Emergence of artemisinin resistance in southeast Asia poses a serious threat to the global control of *Plasmodium falciparum* malaria. Discovery of the K13 marker has transformed approaches to the monitoring of artemisinin resistance, allowing introduction of molecular surveillance in remote areas through analysis of DNA. We aimed to assess the spread of artemisinin-resistant *P falciparum* in Myanmar by determining the relative prevalence of *P falciparum* parasites carrying K13-propeller mutations.

Methods We did this cross-sectional survey at malaria treatment centres at 55 sites in ten administrative regions in Myanmar, and in relevant border regions in Thailand and Bangladesh, between January, 2013, and September, 2014. K13 sequences from *P falciparum* infections were obtained mainly by passive case detection. We entered data into two geostatistical models to produce predictive maps of the estimated prevalence of mutations of the K13 propeller region across Myanmar.

Findings Overall, 371 (39%) of 940 samples carried a K13-propeller mutation. We recorded 26 different mutations, including nine mutations not described previously in southeast Asia. In seven (70%) of the ten administrative regions of Myanmar, the combined K13-mutation prevalence was more than 20%. Geospatial mapping showed that the overall prevalence of K13 mutations exceeded 10% in much of the east and north of the country. In Homalin, Sagaing Region, 25 km from the Indian border, 21 (47%) of 45 parasite samples carried K13-propeller mutations.

Interpretation Artemisinin resistance extends across much of Myanmar. We recorded *P falciparum* parasites carrying K13-propeller mutations at high prevalence next to the northwestern border with India. Appropriate therapeutic regimens should be tested urgently and implemented comprehensively if spread of artemisinin resistance to other regions is to be avoided.

Lancet Infect Dis 2015
Published Online
February 20, 2015
http://dx.doi.org/10.1016/S1473-3099(15)70032-0

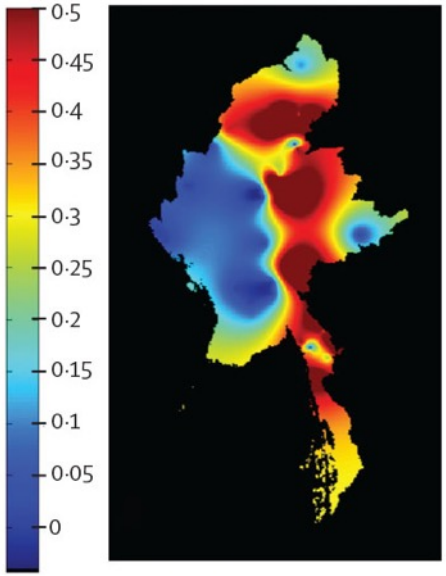
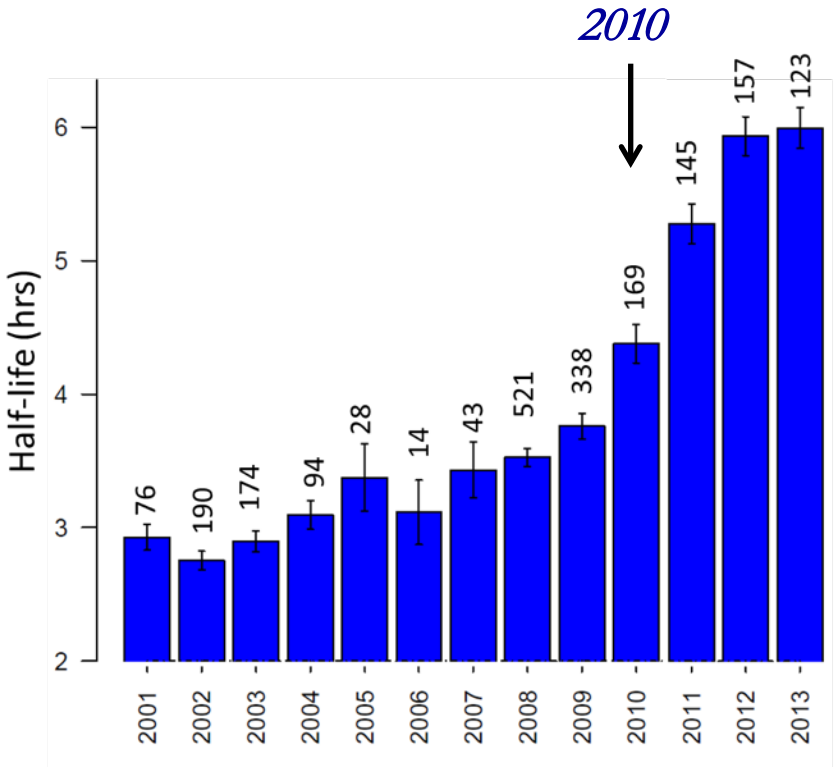


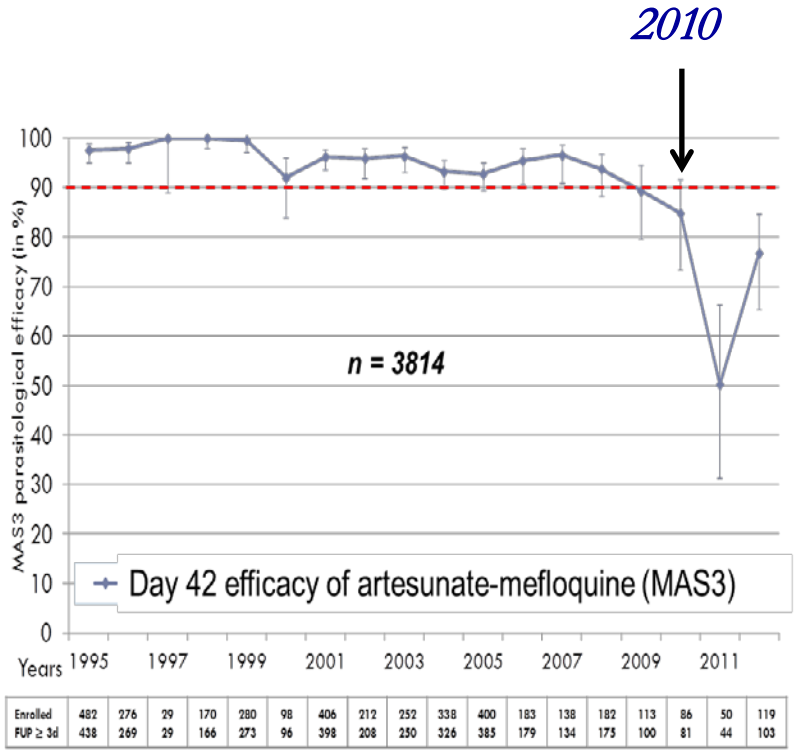
Figure 4: Geographical extent of predicted artemisinin resistance as determined by the prevalence of K13 propeller mutations (>440 aminoacids)

Artemisinin resistance: *selects* for partner drug resistance

2. Thai-Myanmar border



2001-2013

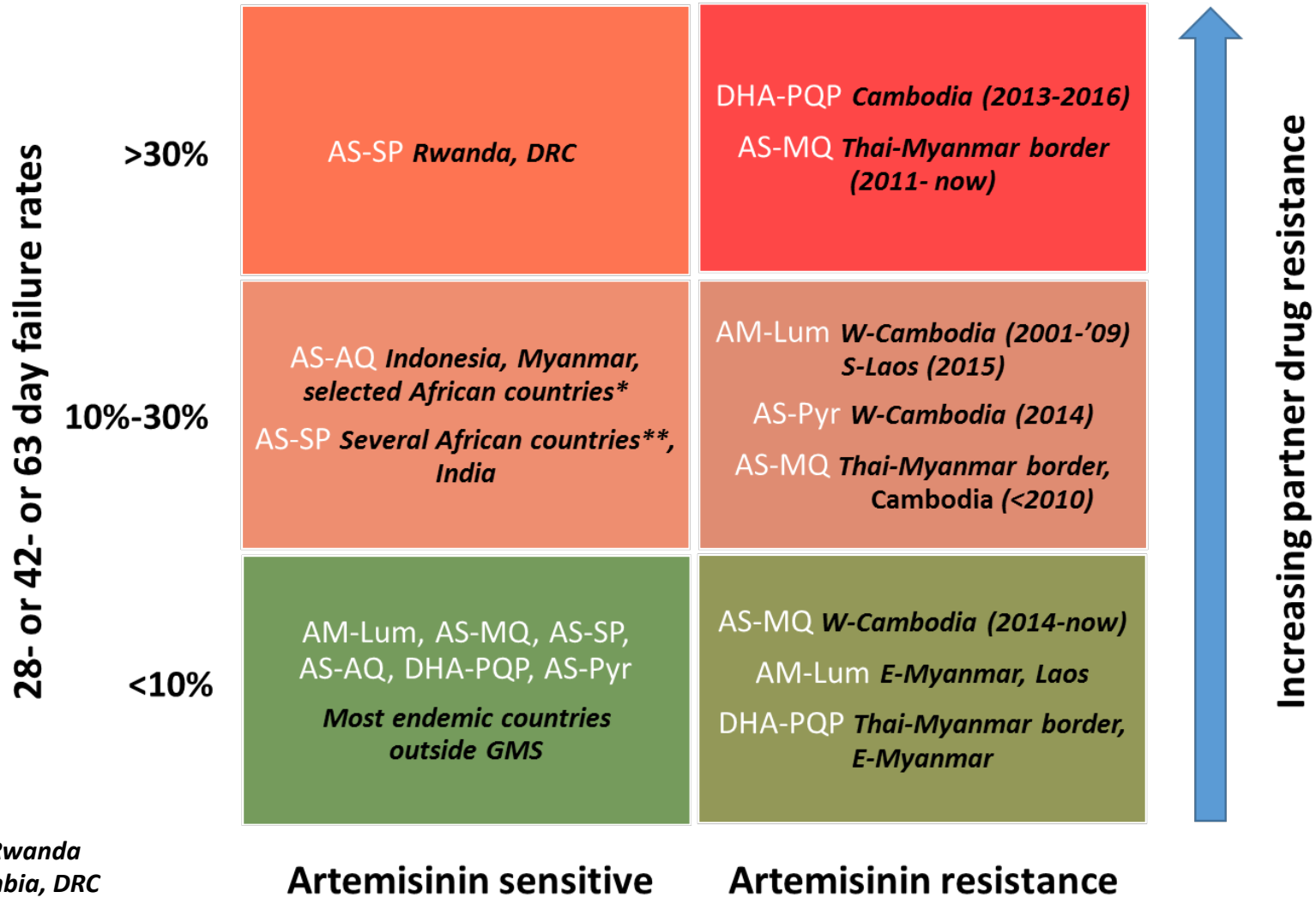


1995-2011

Aung Pyae Phyo et al.
Lancet 2012

Carrara et al.
PLoS Med 2013

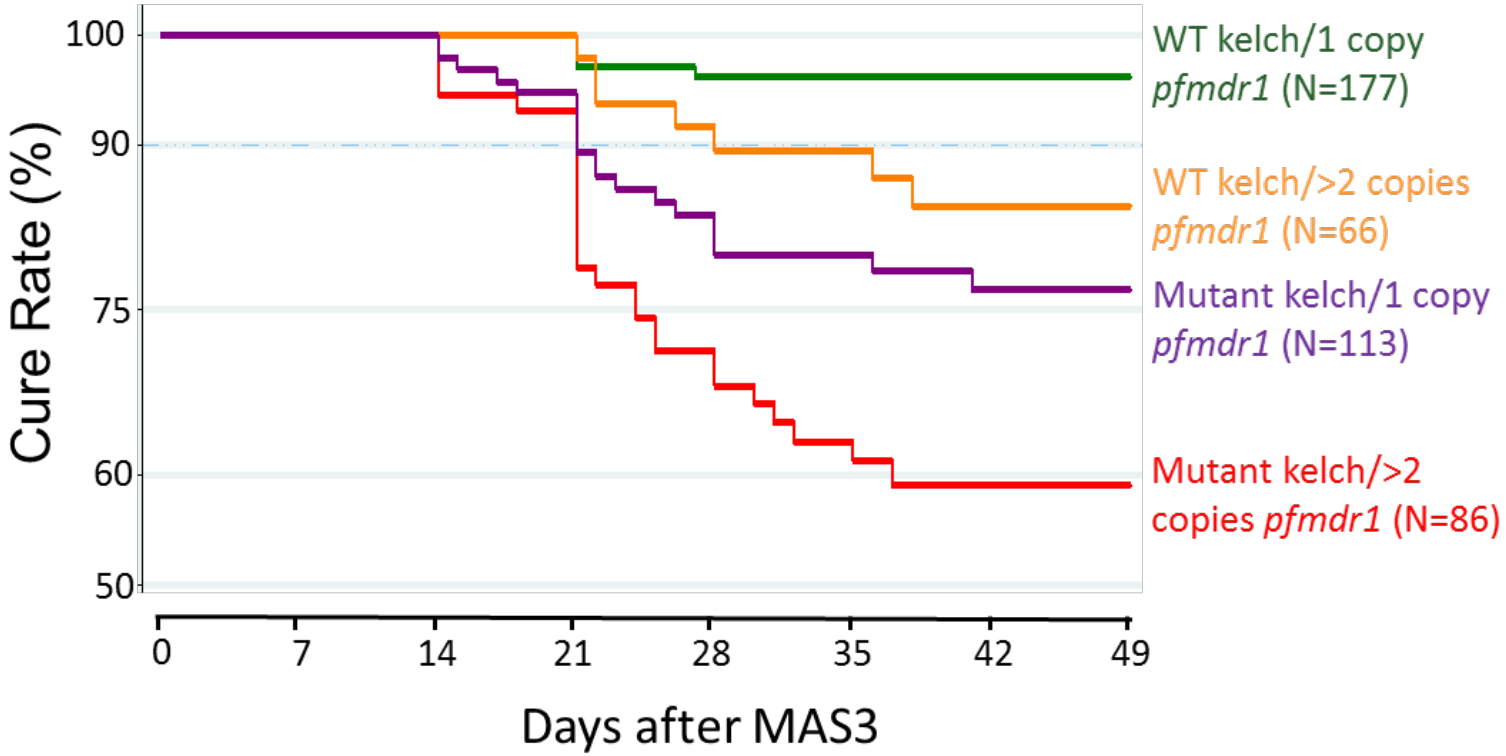
Resistance to artemisinins or partner vs ACT failure



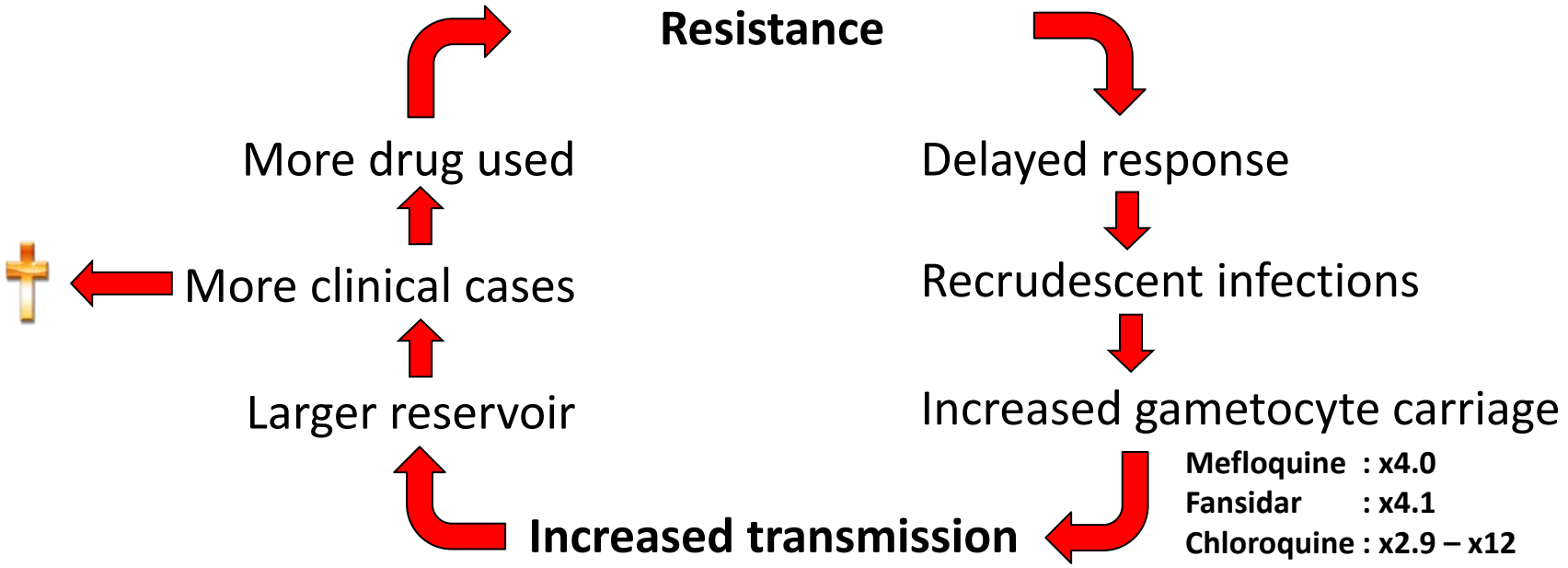
*Burkina Faso, Rwanda
** Rwanda, Zambia, DRC

Artemisinin resistance → treatment failure

after artesunate-mefloquine, also with little MQ resistance



Antimalarial drug resistance ⇒ ↑ transmission

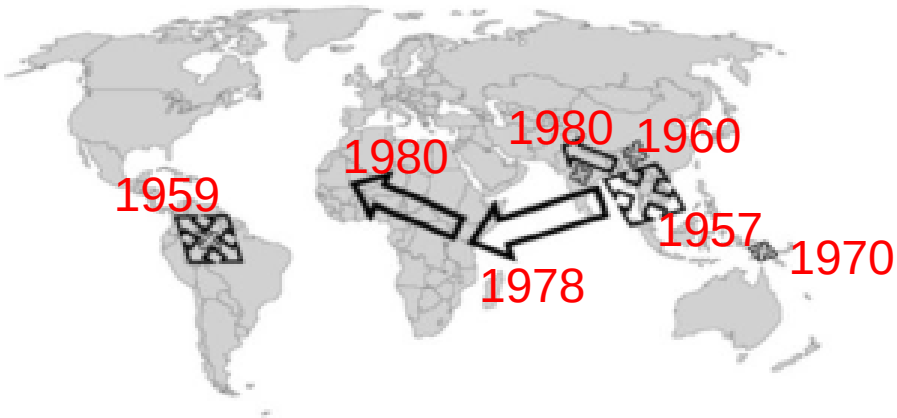


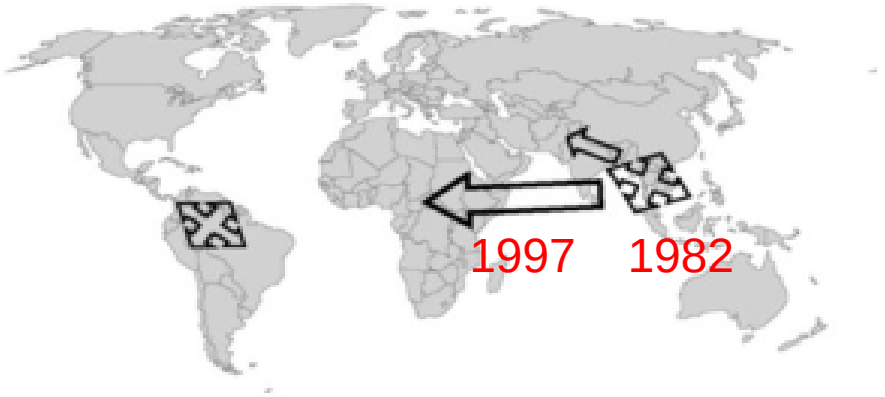
Drakely et al. 2004;
Barnes & White 2005

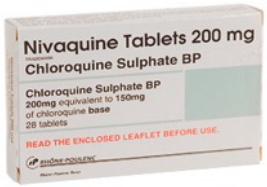
Price et al. 1996; Bousema et al 2003

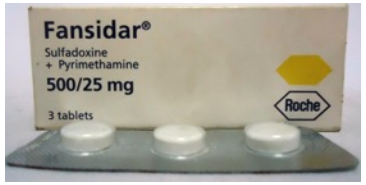
The doom scenario: for artemisinins/ ACTs?

Spread of resistance: chloroquine & pyrimethamine









Dondorp et al
Nat Rev Microbiol. 2010

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Adapted from Chris Plowe

Options with failing ACTs using existing drugs

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

2nd. **Arterolane-piperaquine: *TRAC II***

3rd. **5-day regimen of DHA-PQP or AM-LUM**

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

4th. **Drug rotation of DHA-PQP and MAS3,**

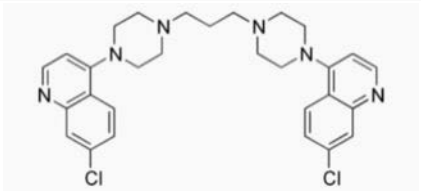
guided by prevalence of PfMDR1 copy-number

5th. **Sequential use of two different ACTs (e.g. DHA-PQP and MAS3)**

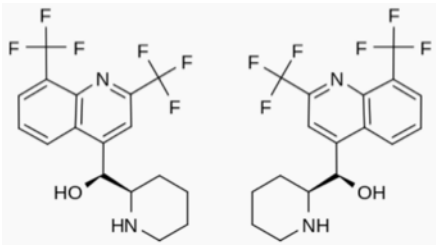
6th. **Artesunate-pyronaridine** efficacy<90%; cross resistance with PQP??

TACT: DHA-piperaquine + mefloquine

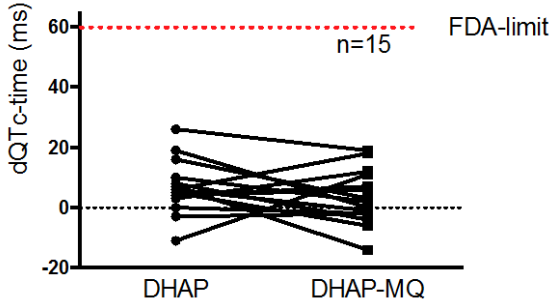
Piperaquine



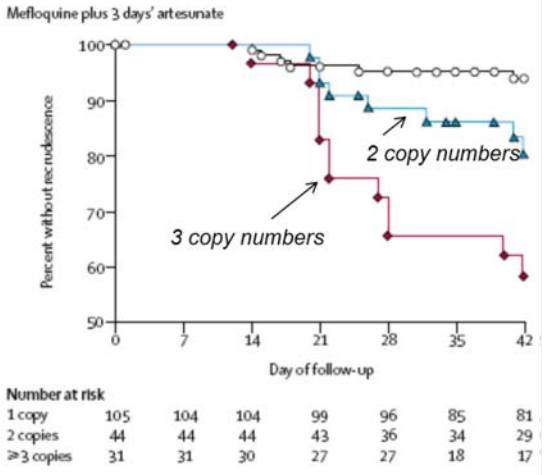
Mefloquine



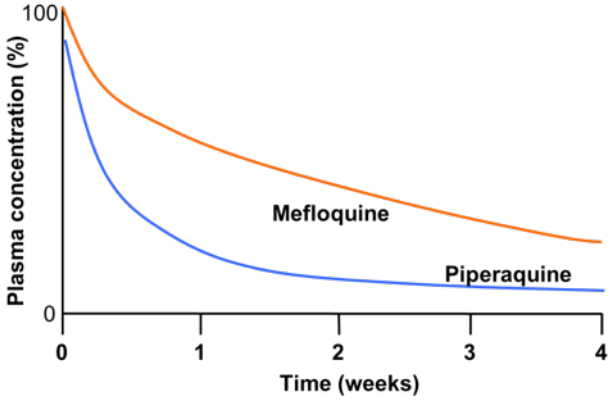
No interaction re QTc time



Possible counter-acting resistance mechanisms



Reasonably matching PK-profiles



Price et al. Lancet 2004

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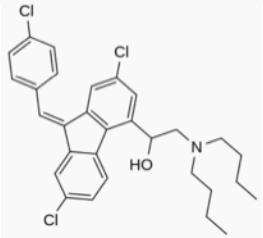
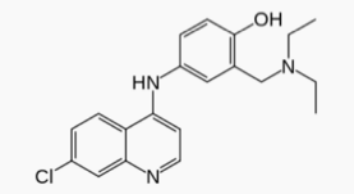
TACT: Artemether-lumefantrine + amodiaquine

Lumefantrine



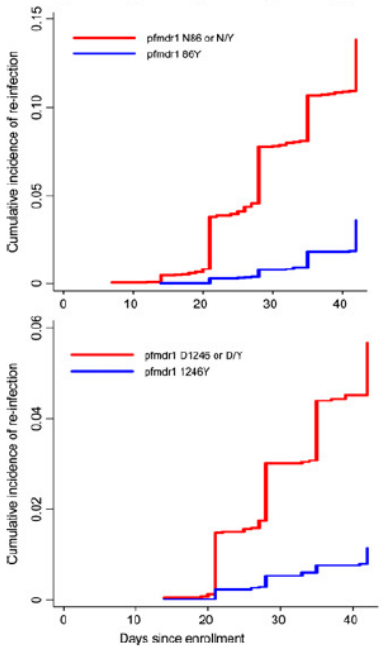
Amodiaquine



Artemether-Lumefantrine

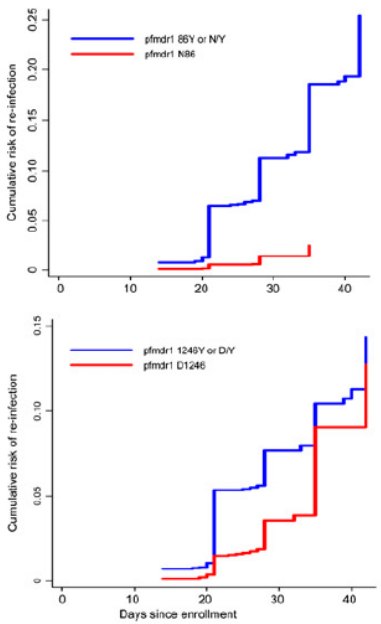
Treatment failure

Artesunate-amodiaquine



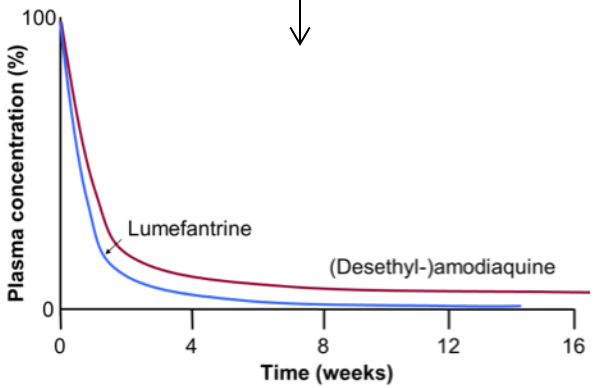
PfMDR1
N86Y

PfMDR1
D1246Y



Counter-acting resistance mechanisms

Reasonably matching PK-profiles



Venkatesan et al.
Am J Trop Med Hyg 2014

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Conclusions: Combination therapy

- Fast acting drug (artemisinin) confers survival advantage
- Partner drug with longer half life permits construction of 3 day regimen
- Combination increases genetic barrier to resistance

- Significantly increases complexity in terms of drug development

Conclusions II: resistance

- Artemisinin resistance now with us:
  - -Expanding in SE Asia; not yet in Africa
  - -Contributes to treatment failure
  - -Selects for partner drug resistance
  - -Might increase transmissibility

- Partner drug resistance:
  - -Increasing problem in SE Asia (Greater Mekong Subregion)

- Few options left in GMS:
  - -Triple combination therapies

- New antimalarials urgently needed!
  - -Choice of partner drug no longer trivial…

Global Portfolio of Antimalarials

Research

Lead optimization

- **DHODH** UTSW/UW/Monash
- **Open Source Drug Discovery** Univ. Sydney
- **Heterocycles** UCT
- **Diversity Oriented Synthesis** Broad/Eisai
- **dUTPase Inhibitors** Medivir
- **Imidazolidine diones** WRAIR
- **Pf NDH2** Imperial College London
- **1 project** Novartis
- **2 projects** GSK
- **Orthologue Leads** Sanofi
- **Tetraoxanes** LSTM/Liverpool
- **Whole cell** St Jude/Rutgers/USF
- **Heterocycles** Celgene
- **Pf NMT** Imperial College London
- **Pantothenamides** TropIQ/RUMC/ Pansynt

Translational

Preclinical

- **P218** (Biotec)
- **DDD498** Merck Serono (Dundee)
- **PA92** (Drexel/UW/GNF)
- **MMV253** (AstraZeneca)
- **GSK030** GSK
- **DSM421** (UTSW/UW/ Monash)
- **AN762** Anacor
- **NPC1161B** Mississippi
- **JPC2997** Jacobus
- **MK4815** Merck

Human volunteers

- **MMV048** UCT/TIA
- **ACT-451840** Actelion
- **CDRI 9778** Ipca
- **N-tert butyl Isoquine** LSTM/Liverpool/GSK
- **SJ733** St Jude/Eisai

Product development

Patient exploratory

- **OZ439/FQ** Sanofi
- **KAE609** Novartis
- **KAF156** Novartis
- **DSM265** UTSW/UW/ Monash
- **Fosmidomycin Piperaquine** Jomaa Pharma/GmbH
- **Methylene Blue/AQ** Heidelberg
- **SAR97276** Sanofi
- **Artemisone** UHKST
- **AQ13** Immtech
- **Sevuparin** Dilaforette

Patient confirmatory

- **Tafenoquine** GSK
- **Dihydroartemisinin - piperaquine Paediatric** Sigma-Tau
- **Co-trimoxazole** ITM Antwerp
- **Artemisinin Naphthoquine** * * KPC
- **Artemether sub-lingual spray** Photo Pharma Ltd

Regulatory review

- **Rectal Artesunate** * Cipla/Strides/WHO-TDR
- **Arterolane/ Piperaquine** Sun Pharmac* *

Access

Post approval

- **Artemether-lumefantrine Dispersible** Novartis 1
- **Artesunate for injection** Guilin 2
- **Dihydroartemisinin-piperaquine** Sigma-Tau 3
- **Pyronaridine-artesunate** Shin Poong 4
- **Pyronaridine-artesunate Paediatric** Shin Poong
- **Artesunate-amodiaquine** * Sanofi/ DNDi 5
- **Artesunate-mefloquine** * Cipla/DNDi
- **SPAQ** Guilin 6

Thank you