Options for treating multidrug resistant falciparum malaria

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March 2018

Overview

1. Status of drug resistance in *Plasmodium falciparum*
2. Treatment options
   a) New drugs?
   b) Longer courses?
   c) Triple combinations?

Artemisia annua

1. Current status of Artemisinin and partner drug resistance

CORRESPONDENCE

Evidence of Artemisinin-Resistant Malaria in Western Cambodia

- 2008: Noedl et al. for the ARC1 Consortium; NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Artemisinin Resistance in *Plasmodium falciparum* Malaria

- 2009: Dondorp et al.; NEJM

ARTICLE

2014

doi:10.1038/nature12876

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

Frédéric Ariey[1,2]†, Benoit Witkowski[3], Chanaki Amaratunga[4], Johann Beghain[1,2]†, Anne-Claire Langlois[1,2], Nimol Khim[3], Saorin Kim[3], Valentine Duru[3], Christiane Bouchier[5], Laurence Ma[5], Pharath Lim[3,4,6], Rithea Leang[6], Socheat Duong[6], Sokunthea Sreng[6], Seila Suon[6], Char Meng Chuor[6], Denis Mey Bout[7], Sandie Ménard[8]†, William O. Rogers[9], Blaise Genton[10], Thierry Fandeur[1,3], Olivo Miotto[11,12,13], Pascal Ringwald[14], Jacques Le Bras[15], Antoine Berry[8]†, Jean-Christophe Barale[1,2]†, Rick M. Fairhurst[4]*, Françoise Benoit-Vical[16,17]*, Odile Mercereau-Puijalon[1,2]* & Didier Ménard[3]*

*kelch*13

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*kelch*13

e.g. C580Y

Partner drug resistance (ACT failures)

- DHA-piperaquine failure rates of ~ 50% in Cambodia and Viet Nam
- AS-MQ failure rates of ~ 20% on the Thai-Myanmar border

Thanh *et al. Malar J* (2017) 16:27
DOI 10.1186/s12936-017-1680-8

Malaria Jour

RESEARCH Open Acc

Rapid decline in the susceptibility of *Plasmodium falciparum* to dihydroartemisinin–piperaquine in the south of Vietnam

Ngo Viet Thanh[1], Nguyen Thuy-Nhien[1*], Nguyen Thi Kim Tuyen[1], Nguyen Thanh Tong[1], Nguyen Thuy Nha-Ca[1], Le Thanh Dong[2], Huynh Hong Quang[3], Jeremy Farrar[1,4], Guy Thwaites[1,4], Nicholas J. White[4,5], Marcel Wolbers[1,4] and Tran Tinh Hien[1,4]

Clinical Infectious Diseases

MAJOR ARTICLE

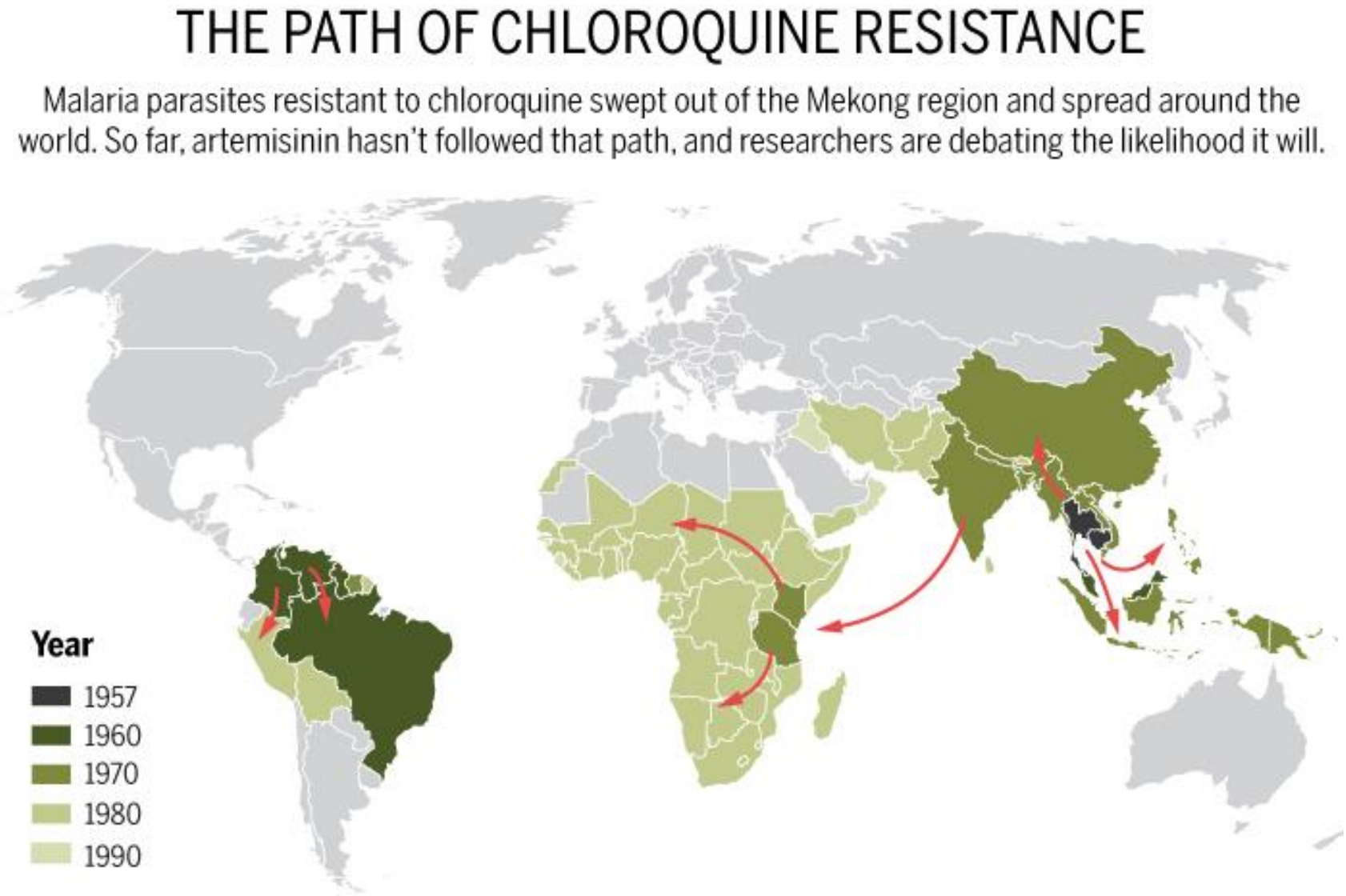
IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Declining Efficacy of Artemisinin Combination Therapy Against *P. Falciparum* Malaria on the Thai–Myanmar Border (2003–2013): The Role of Parasite Genetic Factors

Aung Pyae Phyo,[1,2] Elizabeth A. Ashley,[1,2,3] Tim J. C. Anderson,[4] Zbynek Bozdech,[5] Verena I. Carrara,[1,3] Kanlaya Sriprawat,[1] Shalini Nair,[4] Marina McDew White,[4] Jerzy Dziekan,[5] Clare Ling,[1,2,3] Stephane Proux,[1] Kamonchanok Konghahong,[1] Atthanee Jeeyapant,[3] Charles J. Woodrow,[2,3] Mallika Imwong,[3] Rose McGready,[1,2] Khin Maung Lwin,[1,3] Nicholas P. J. Day,[2,3] Nicholas J. White,[2,3] and Francois Nosten[1,2]

[1]Shoklo Malaria Research Unit, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Mae Sot, Thailand; [2]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, United Kingdom; [3]Mahidol Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [4]Department of Genetics, Texas Biomedical Research Institute, San Antonio; and [5]Division of Molecular Genetics & Cell Biology, School of Biological Sciences, Nanyang Technological University, Singapore

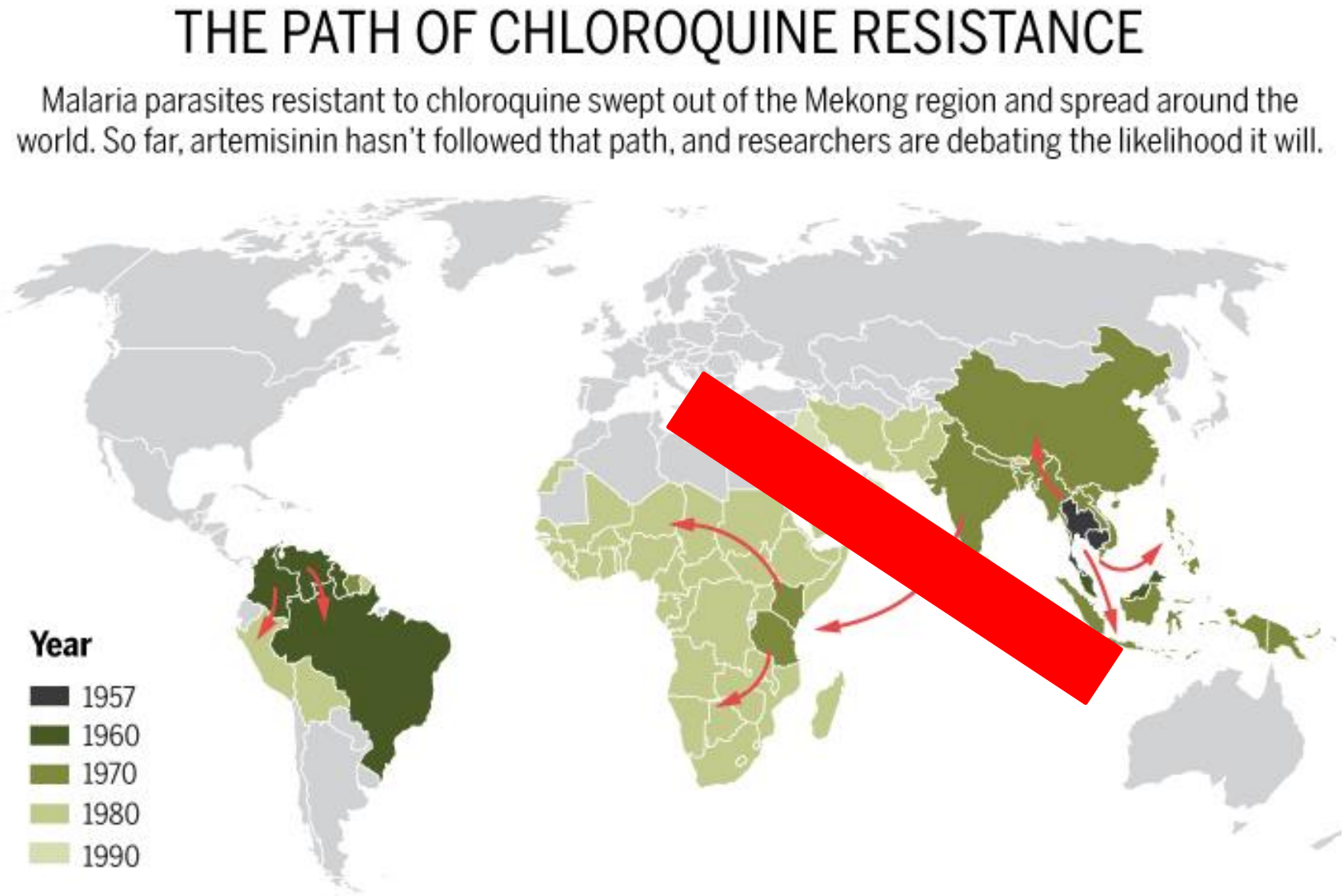
Can it be stopped?



Science 2016

doi:10.1126/science.aaf9947

Can it be stopped?

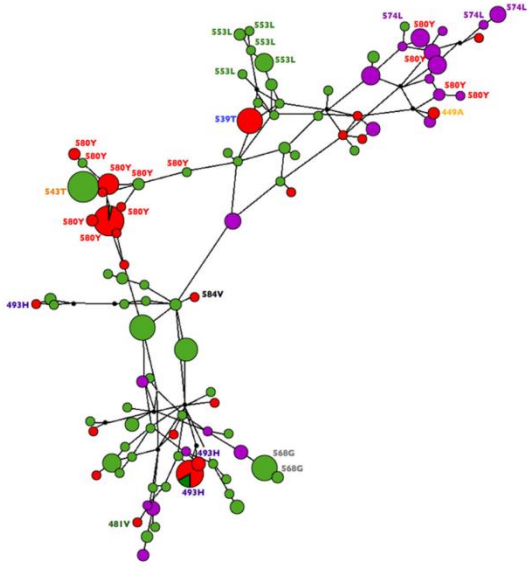


Science 2016

doi:10.1126/science.aaf9947

“Popping” or spread?

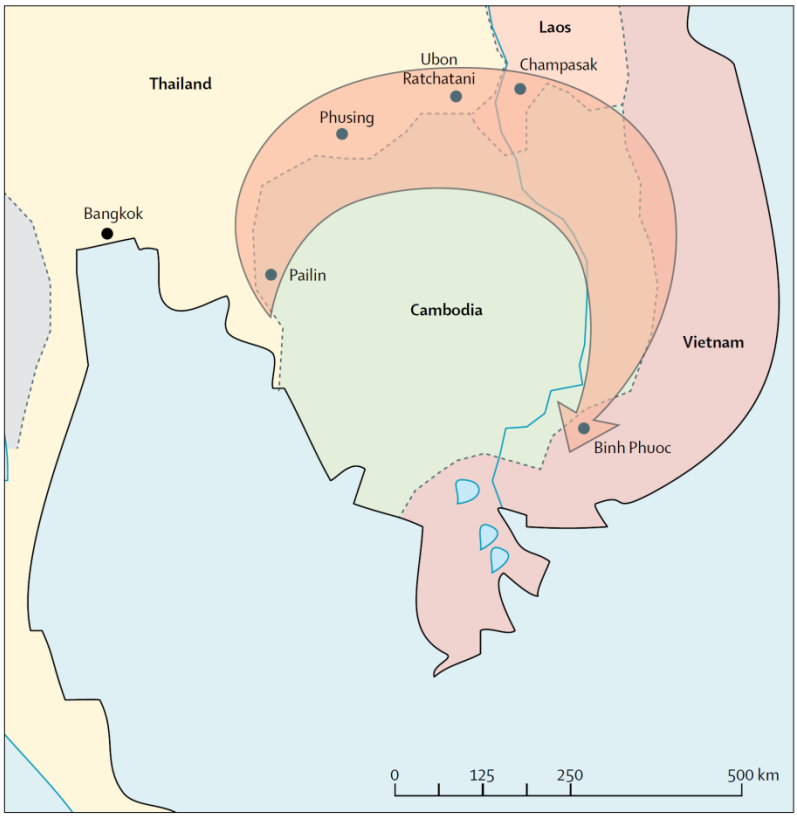
- Haplotype analysis has shown ***independent emergence*** of the same artemisinin-resistance mutations in different geographical areas in Southeast Asia,
  - e.g. C580Y emerged once in the east (Cambodia/Vietnam) and once in the West (Myanmar)



Takala-Harrison, JID 2015

Super-malaria?

- Transnational spread of multidrug resistant *P.falciparum* *kelch*C580Y lineage
  - Detected first in Pailin in 2008
  - It later acquired **piperaquine resistance** and spread east.
  - Now found in Cambodia, Thailand, Laos, Vietnam

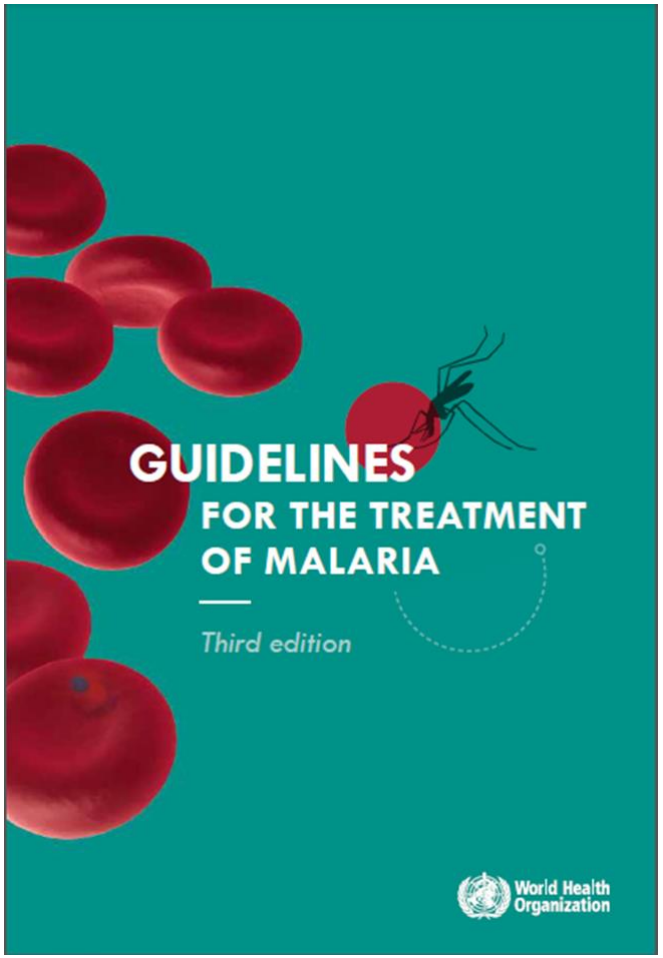


Imwong et al. Spread of a single multidrug resistant malaria parasite lineage (PfPailin) to Vietnam; LID, 2017

2017

2. Options for treatment (endemic countries)

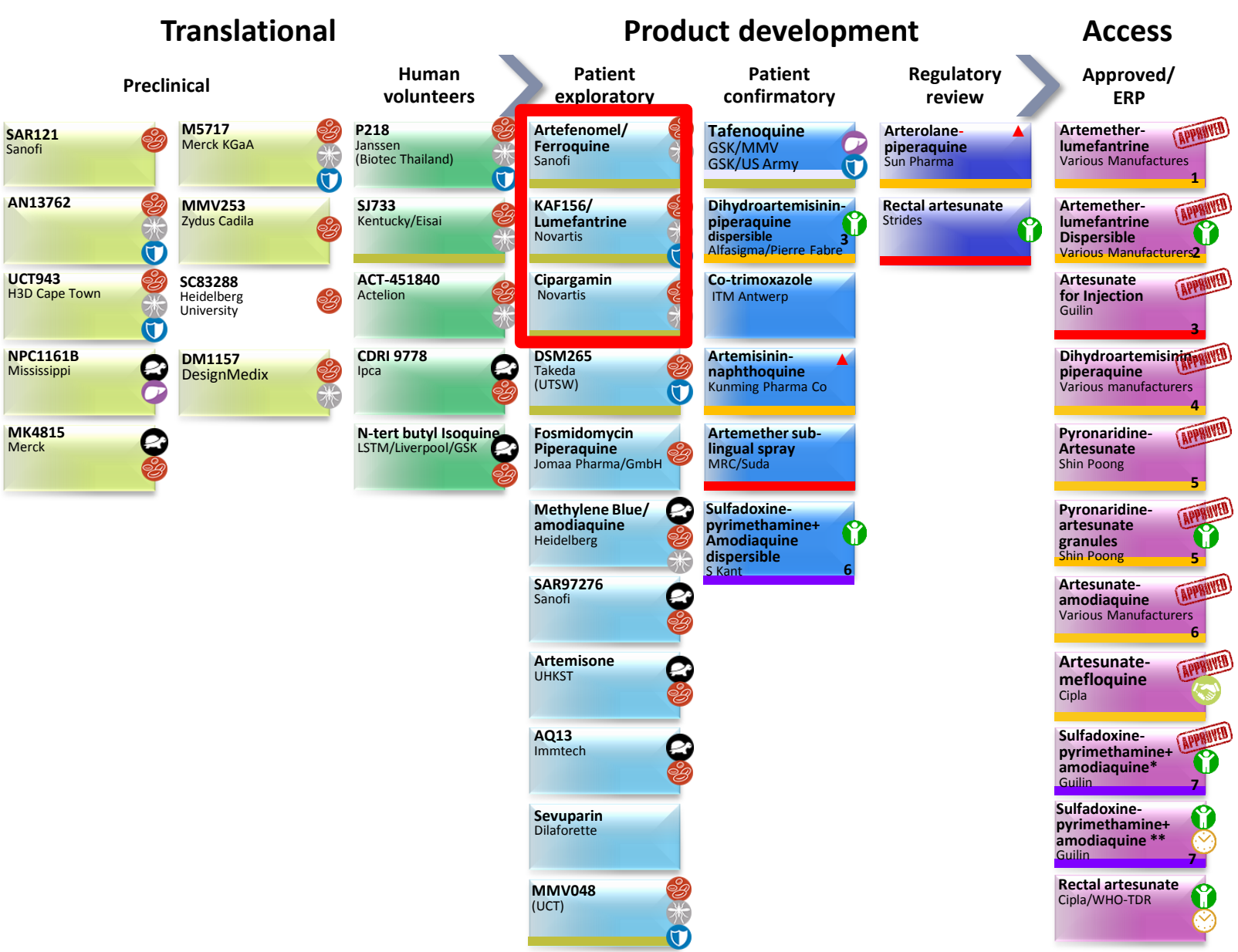
a. New drugs?
b. Recycle old drugs
c. Longer ACT courses
d. Triple ACTs



a. New antimalarial drugs

- Success rates for drugs in Phase 2 are 34-60%
- Success rates for drugs in preclinical phase are 8%

(Burrows et al. Malaria Journal 2017)


Translational
Product development
Access
Preclinical
Human volunteers
Patient exploratory
Patient confirmatory
Regulatory review
Approved/ ERP
SAR121
Sanofi
AN13762
UCT943
H3D Cape Town
NPC1161B
Mississippi
MK4815
Merck
M5717
Merck KGaA
MMV253
Zydus Cadila
SC83288
Heidelberg University
DM1157
DesignMedix
P218
Janssen (Biotec Thailand)
SJ733
Kentucky/Eisai
ACT-451840
Actelion
CDRI 9778
Ipca
N-tert butyl Isoquine
LSTM/Liverpool/GSK
Artefenomel/ Ferroquine
Sanofi
KAF156/ Lumefantrine
Novartis
Cipargamin
Novartis
DSM265
Takeda (UTSW)
Fosmidomycin Piperaquine
Jomaa Pharma/GmbH
Methylene Blue/ amodiaquine
Heidelberg
SAR97276
Sanofi
Artemisone
UHKST
AQ13
Immtech
Sevuparin
Dilaforette
MMV048
(UCT)
Tafenoquine
GSK/MMV GSK/US Army
Dihydroartemisinin-piperaquine dispersible
Alfasigma/Pierre Fabre
3
Co-trimoxazole
ITM Antwerp
Artemisinin-naphthoquine
Kunming Pharma Co
Artemether sub-lingual spray
MRC/Suda
Sulfadoxine-pyrimethamine+ Amodiaquine dispersible
S Kant
6
Arterolane-piperaquine
Sun Pharma
Rectal artesunate
Strides
Artemether-lumefantrine
Various Manufactures
1
Artemether-lumefantrine Dispersible
Various Manufacturers
2
Artesunate for Injection
Guilin
3
Dihydroartemisinin-piperaquine
Various manufacturers
4
Pyronaridine-Artesunate
Shin Poong
5
Pyronaridine-artesunate granules
Shin Poong
5
Artesunate-amodiaquine
Various Manufacturers
6
Artesunate-mefloquine
Cipla
Sulfadoxine-pyrimethamine+ amodiaquine*
Guilin
7
Sulfadoxine-pyrimethamine+ amodiaquine **
Guilin
7
Rectal artesunate
Cipla/WHO-TDR
APPROVED

Leading candidates in clinical development

- Artefenomel+ferroquine
- Lumefantrine + KAF-156
- Cipargamin

Artefenomel+ferroquine

- Artefenomel (previously OZ439) a long-acting synthetic ozonide
- Ferroquine(FQ)- long-acting aminoquinoline (half-life 16 days)
- Targeting single dose treatment
- Multicentre dose-finding phase 2b study (NCT02497612) is underway

Artefenomel+ferroquine

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- Multicentre dose-
  (NCT02497612) is underw

How much cross-resistance is there between artefenomel and artemisinin derivatives?

Lumefantrine-KAF156

- KAF156: highly potent imidazolopiperazine which has multistage activity
- Lumefantrine: an arylaminoalcohol already in widespread use combined with artemether
- Phase 3 dose-finding study ongoing in West Africa (NCT03167242)
- Targeting single dose treatment/radical cure

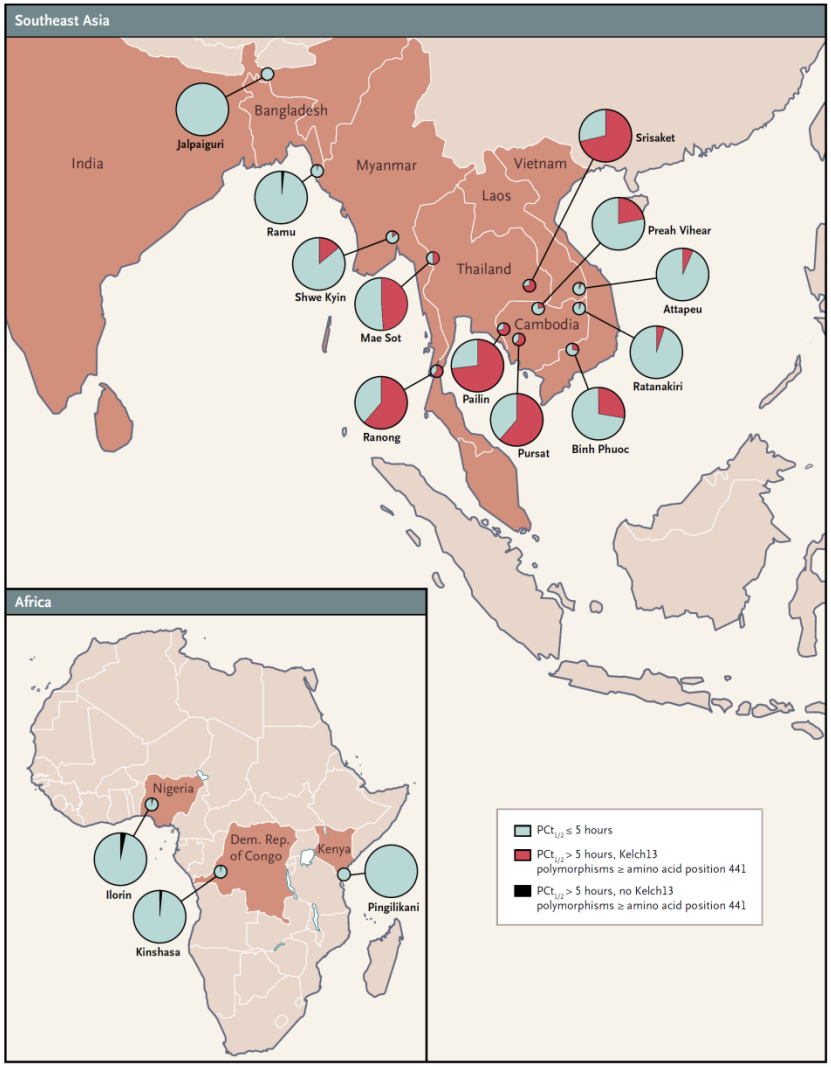
Cipargamin

- Spiroindolone
- PfATP4 inhibitor
- Potent, long-acting blood schizonticide
- Dose-escalation safety study is recruiting in Mali (NCT03334747) with a special focus on hepatotoxicity after signals in earlier studies

b. Prolonged ACT courses

- Artemisinin derivatives still work- just much less well
  - Non-response to treatment not described

- Giving longer courses can improve efficacy



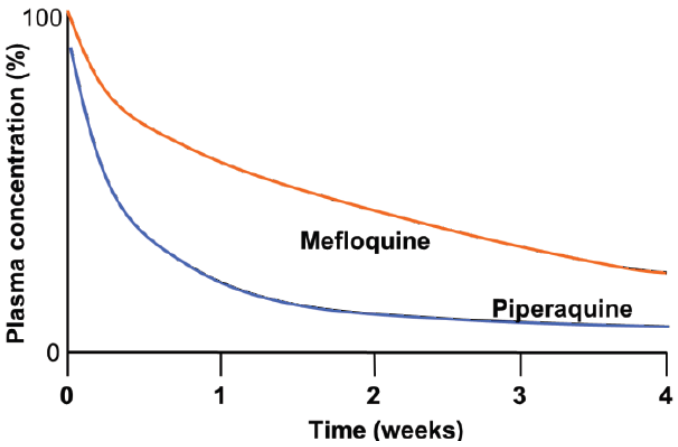
TRAC study; NEJM 2014

Day 42 Efficacy of 6 day treatments

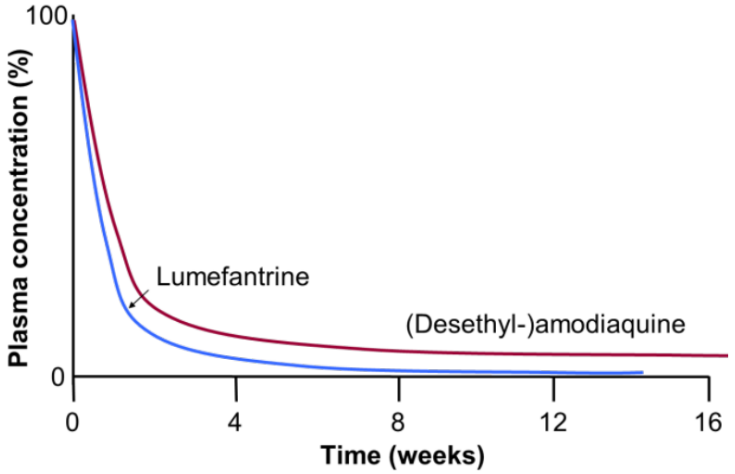
Site	Treatment	Duration (days)	N recurrences/ N patients	PCR-corrected efficacy [95% CI] @ D42
Cambodia-Pailin	AS4 + DP	6	2/100	97.7 [90.9-99.4]
Viet Nam-Binh Phuoc	AS2+DP	6	0/60	100 [93.2-100]
Viet Nam-Binh Phuoc	AS4+DP	6	0/60	100 [93.0-100]
Laos-Attapeu	AS4+AL	6	2/60	100 [93.5-100]
Myanmar-Shwe Kyin	AS4+AL	6	0/40	100 [87.9-100]

b. Triple Artemisinin-based combinations

DHA-piperaquine and mefloquine

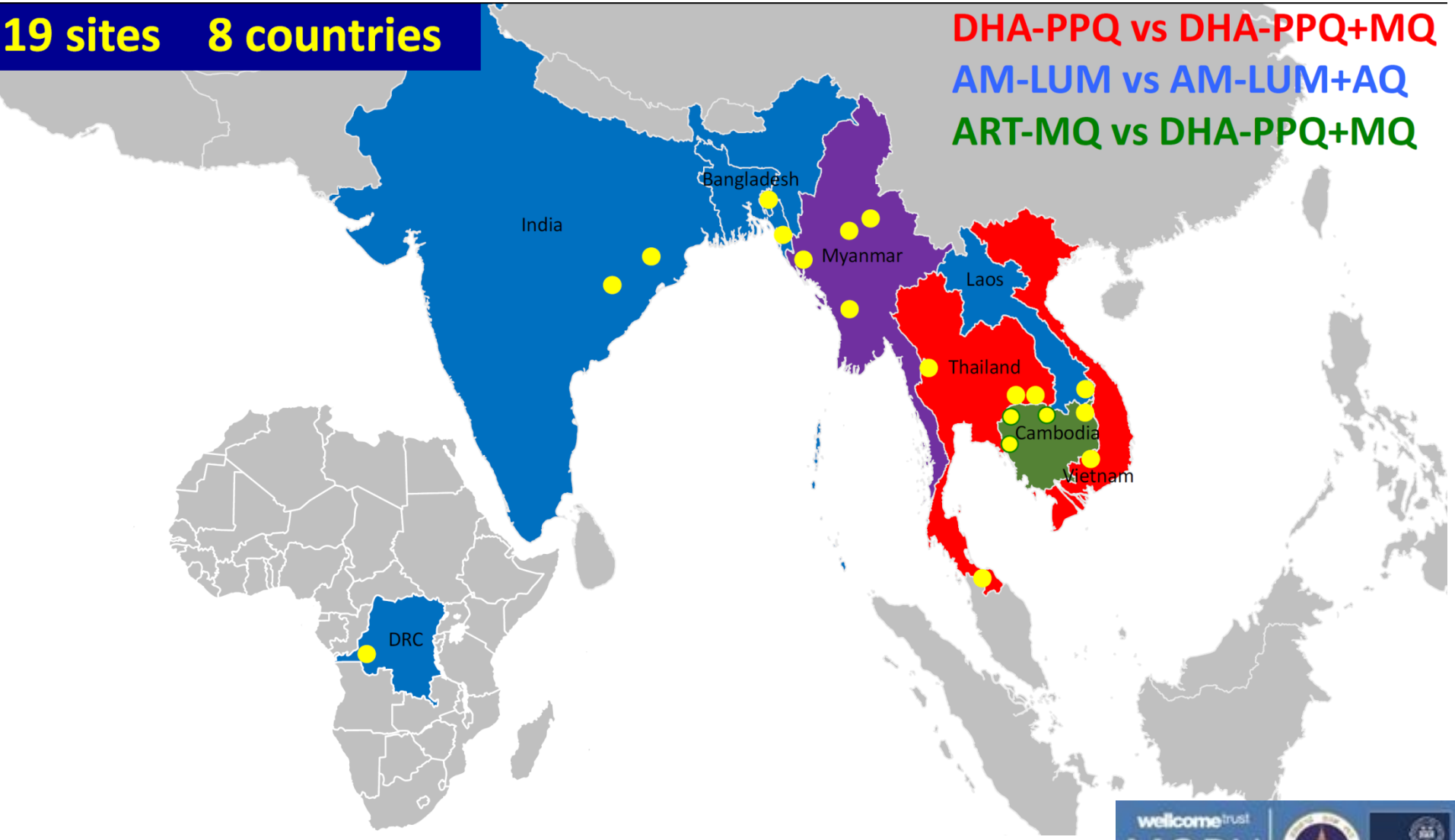


Artemether-lumefantrine and amodiaquine



- Fairly well matched elimination kinetics
- Opposing resistance selection effects?

TRAC 2 study: RCT (120 patients/site)



wellcome trust MORU Tropical Health Network OXFORD

Aims

1. Update on status of artemisinin and partner drug resistance
   i. Phenotypic (parasite clearance half-life > 5h)
   ii. Genotypic (*kelch*13, plasmepsin, pfmdr1)
2. Efficacy of ACTs and triple-ACTs
3. Safety and tolerability of triple ACTs

Key inclusion & exclusion criteria

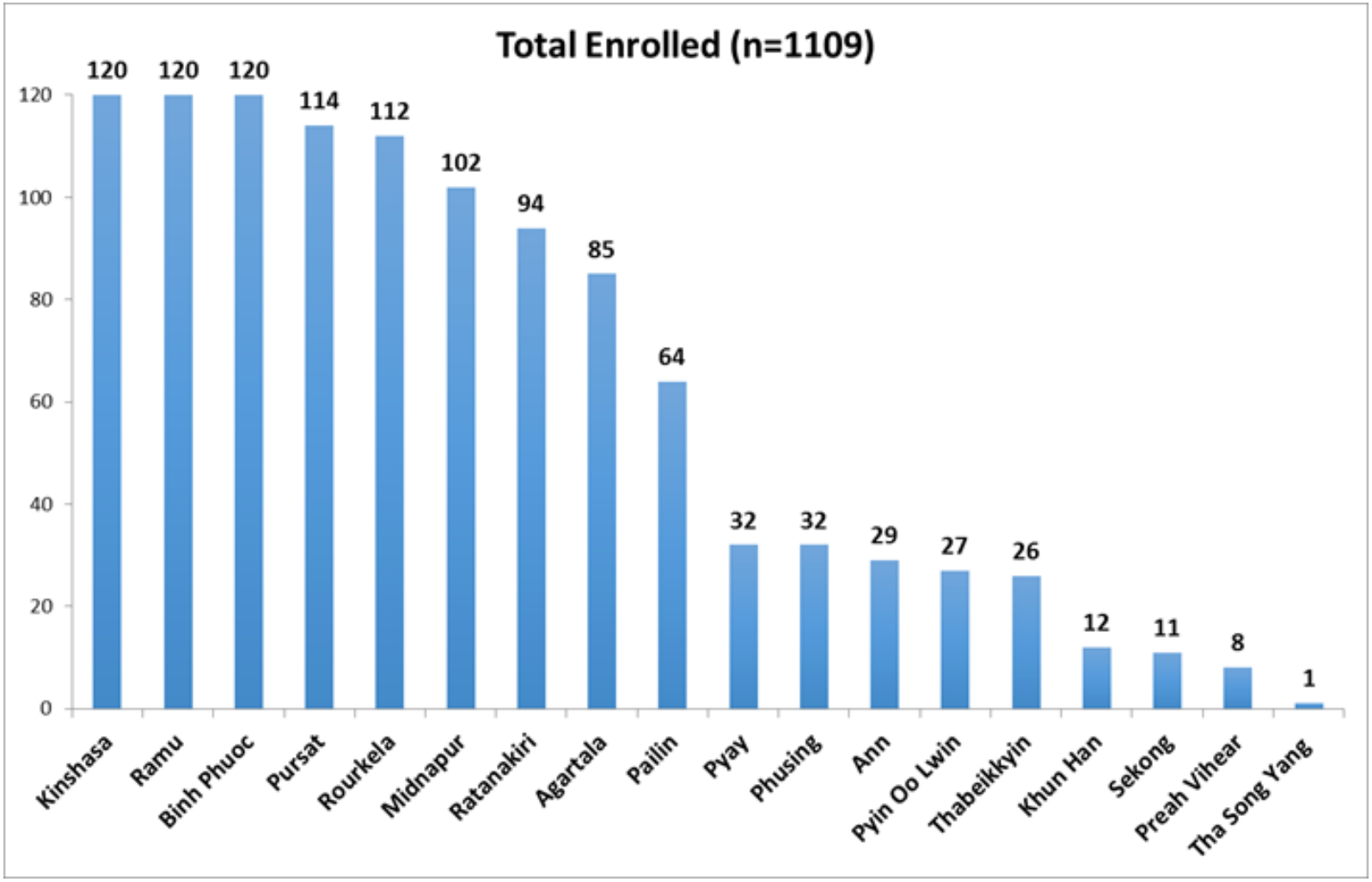
Inclusion criteria

- Male or female, aged from 6 months to 65 years old.
- Symptomatic acute uncomplicated *P. falciparum* malaria, with asexual parasite density of 5,000 to 200,000/µL
- Written informed consent

Exclusion criteria

- Severe/complicated malaria
- Haematocrit < 25% or Hb < 8 g/dL
- For females: pregnancy, breast feeding
- ACT treatment within the previous 7 days or mefloquine within 2 months
- History of cardiac disease

Recruitment halted- January 2018



Preliminary conclusions

- Poor efficacy of DHA-piperaquine in Northeastern Thailand, Cambodia and Southwest Vietnam
- Good efficacy of the two Triple ACTs in sites with failing DHA-piperaquine
- Reassuring tolerability and safety so far but more data needed

But……

Is it already too late?

Emergence of *Plasmodium falciparum* triple mutant in Cambodia

- Kelch13 C580Y (artemisinin)
- Pfmdr copy no. (mefloquine)
- Plasmepsin2 copy no. (piperaquine)

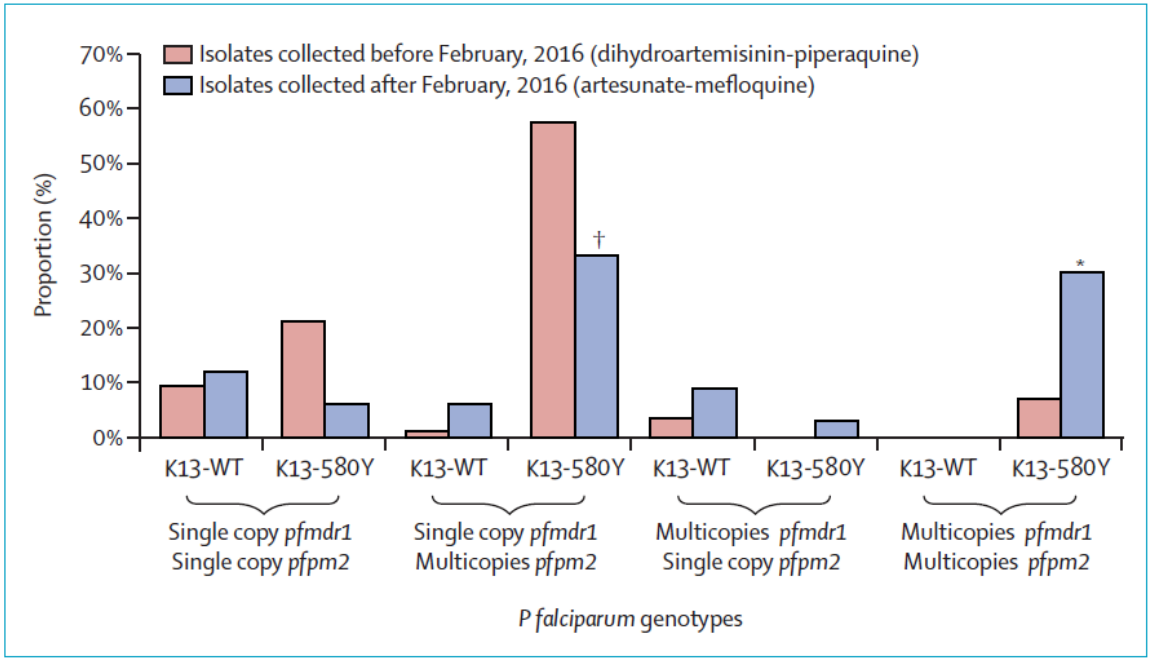


Figure: **Temporal increase in the proportion of *Plasmodium falciparum* triple mutants**

Rossi et al.; Lancet Infectious Diseases, December 2017

Next steps

- Evaluation of artemether-lumefantrine+ amodiaquine in Vietnam/Cambodia
- Development co-blistered triple ACTs
- Large trial focused on safety and tolerability in Africa and Asia
- Development fixed dose TACTs
  - with existing drugs?
  - with new compounds?

Acknowledgements

- Rob van der Pluijm (TRAC 2 coordinator)
- Arjen Dondorp (TRAC2 PI)
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- TRAC 2 was funded by

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- ISID