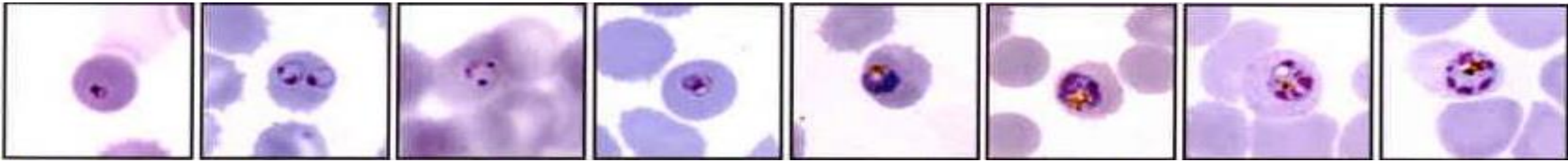
Triple Artemisinin-Based Combination Therapies

to treat and prevent multidrug resistant *falciparum* malaria



RBM meeting
Kigali, Rwanda
18 May 2022

Arjen Dondorp
Mahidol-Oxford Tropical Medicine Research Unit
Bangkok, Thailand

Artemisinin-based Combination Therapies (ACT)

Artemether-lumefantrine

Artesunate-mefloquine

Dihydroartemisinin-piperaquine

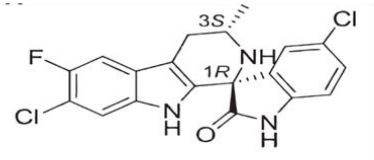
Artesunate-amodiaquine

Artesunate-sulphadoxine-pyrimethamine

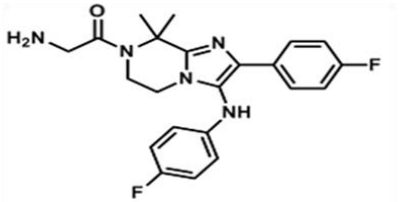
Artesunate-pyronaridine

New antimalarial drugs under development

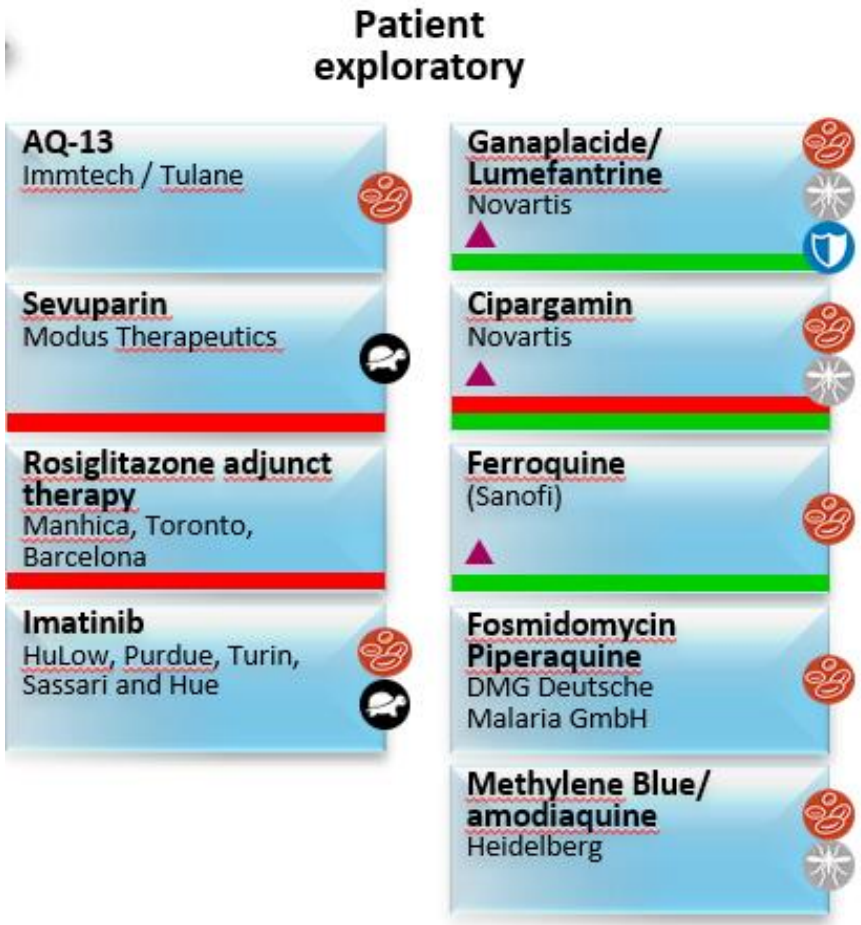
- **Spiroindolones**
  (KAE609; Cipargamin)



- **Imidazolopiperazine**
  (KAF156, Ganaplacide)



Disappeared from the list in the last year:
OZ439 (Artefenomel), DSM265, MMV048

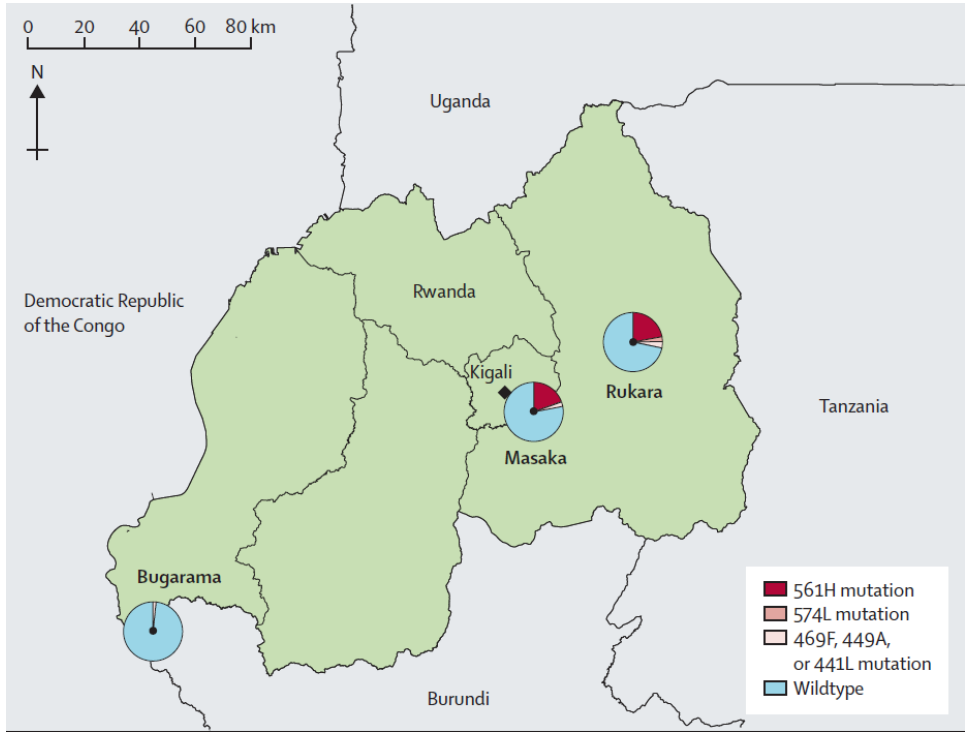


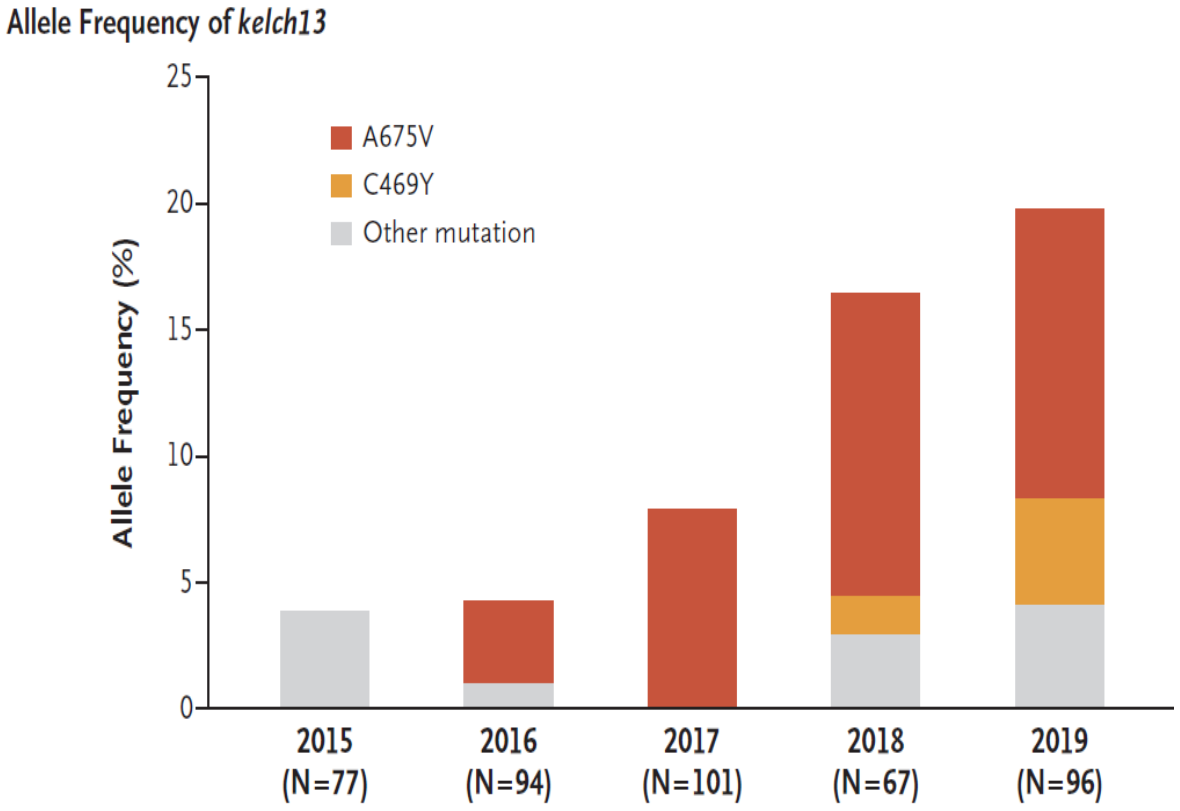
…all >4 years away from registration

MMV website

Independent emergence of artemisinin resistance in Africa

Rwanda, Uganda, Horn of Africa





Uwimana et al. *Lancet Infect Dis 2021*
Uwimana et al. *Nature Med 2020*

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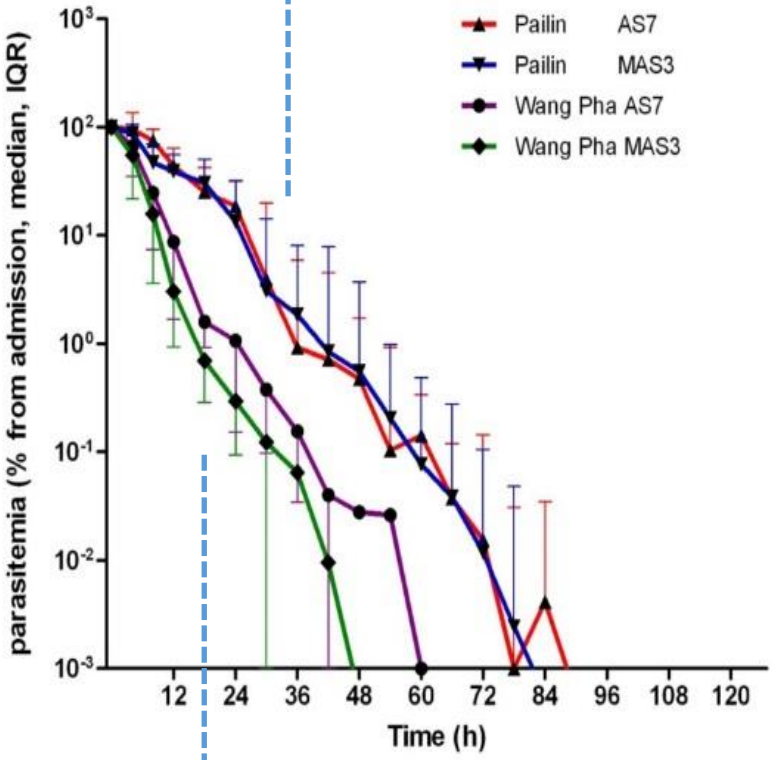
Balikagala et al. *N Engl J Med 2021*

Potential impact of artemisinin resistance in the African context

- Still high efficacy of ACTs
  - no high-grade artemisinin resistance anywhere yet
  - higher transmissibility of artemisinin resistant *P. falciparum*(?)
- But: facilitates partner drug resistance
  - if resistance to both components: ↓↓ efficacy
- Reduced efficacy i.v. artesunate for severe malaria?

Cut-off different for Africa

Partial resistant: $PC_{1/2}$ > 5 hours



Sensitive: $PC_{1/2}$ < 5 hours

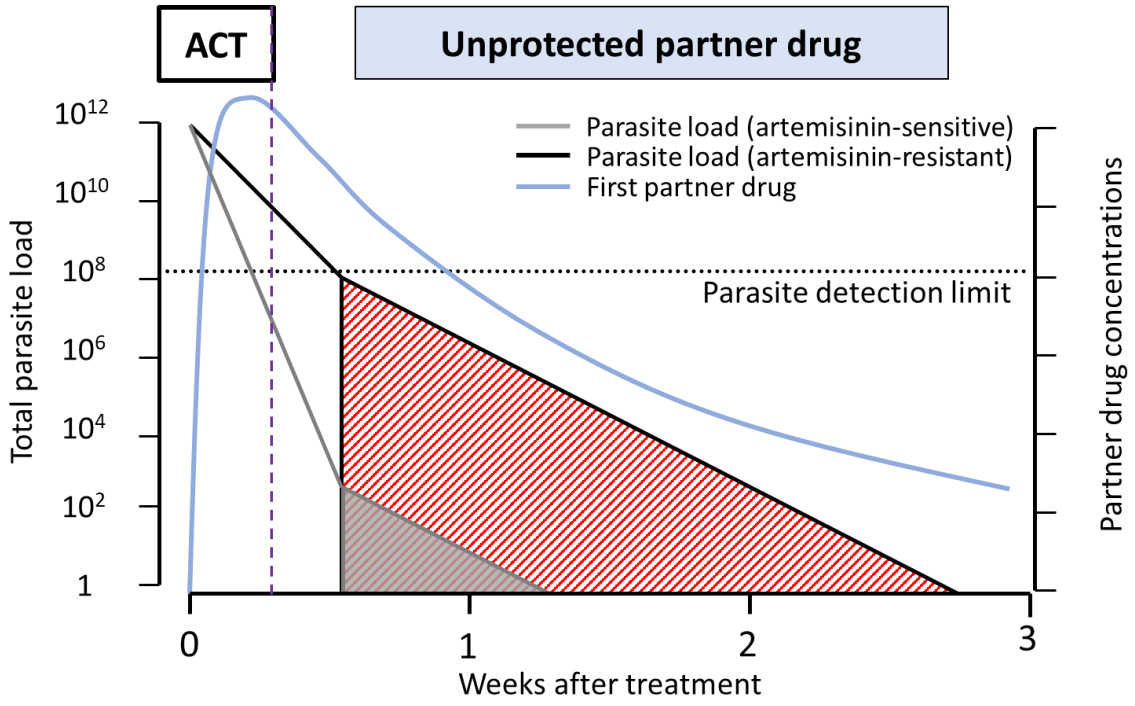
Dondorp et al. N Eng J Med 2009

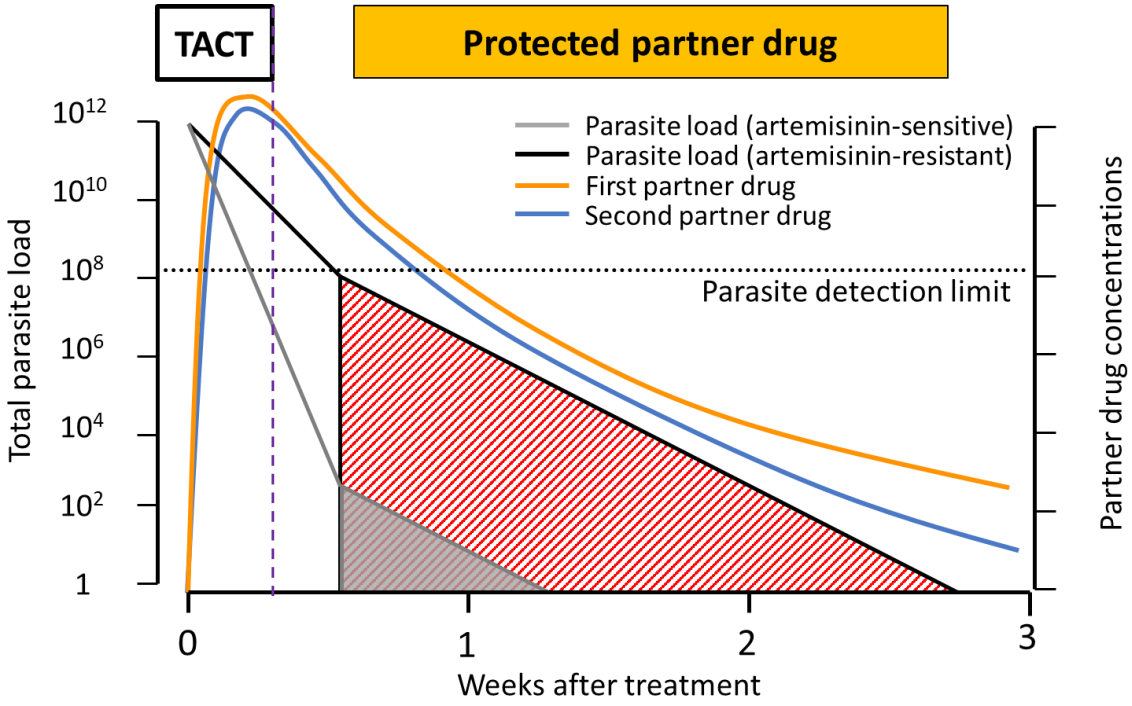
Containment of artemisinin resistance in the African context- pharmacological interventions

1. Non-artemisinin based new drugs (≥ 5 years from now)
2. Multiple first line treatments
3. **Triple therapies (TACT): AS/DHA-PPQ-MQ; AM-LUM-AQ; Arterolane-PPQ-MQ; AS-Pyr-Atovaquone-Proguanil**
4. ? Prolonged ACT regimens: 5 days of AM-LUM
5. ? Sequential use of two different ACTs (e.g. ASAQ and AL)

And: implementation of gametocytocidal single low-dose primaquine

Triple Artemisinin Combination Therapy (TACT) (or 'enhanced ACTs')

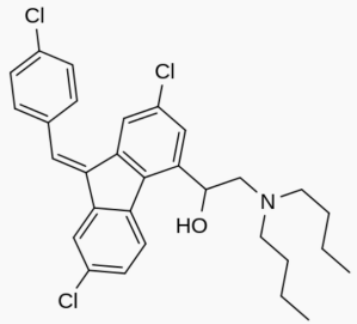




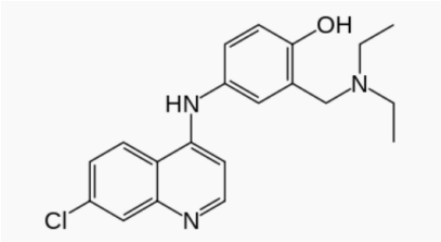
Van der Pluijm et al. *Trends Parasit 2020*

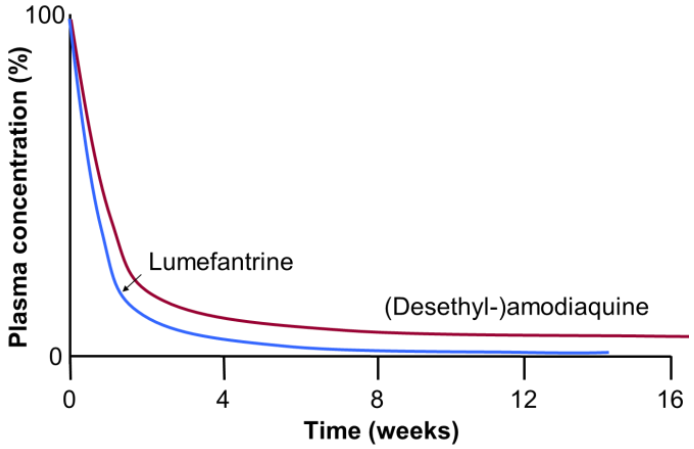
TACT: artemether-lumefantrine + amodiaquine

Lumefantrine



Amodiaquine

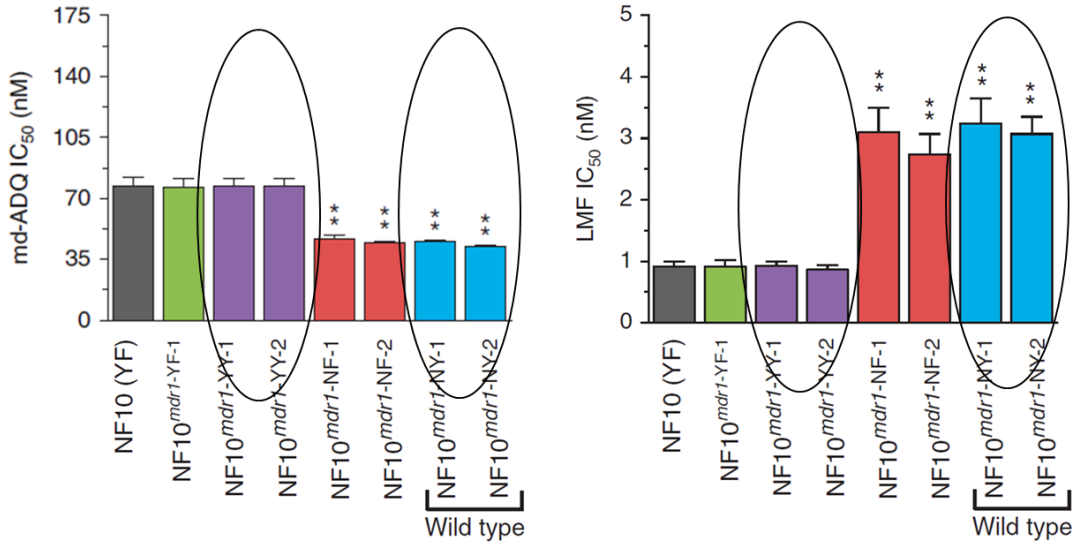




Matching PK-profiles

NF10
(PfCRT CVIET - SE Asia/Africa)

fMDR1
N86Y

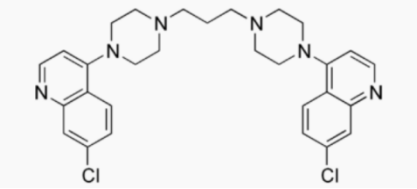


Counteracting resistance mechanisms

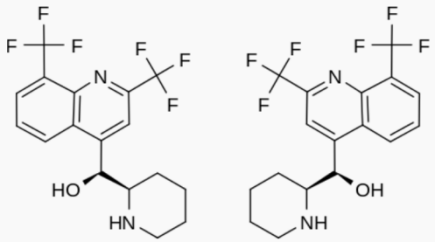
Veiga et al. Nature Commun 2016

TACT: DHA (or artesunate)-piperaquine+mefloquine

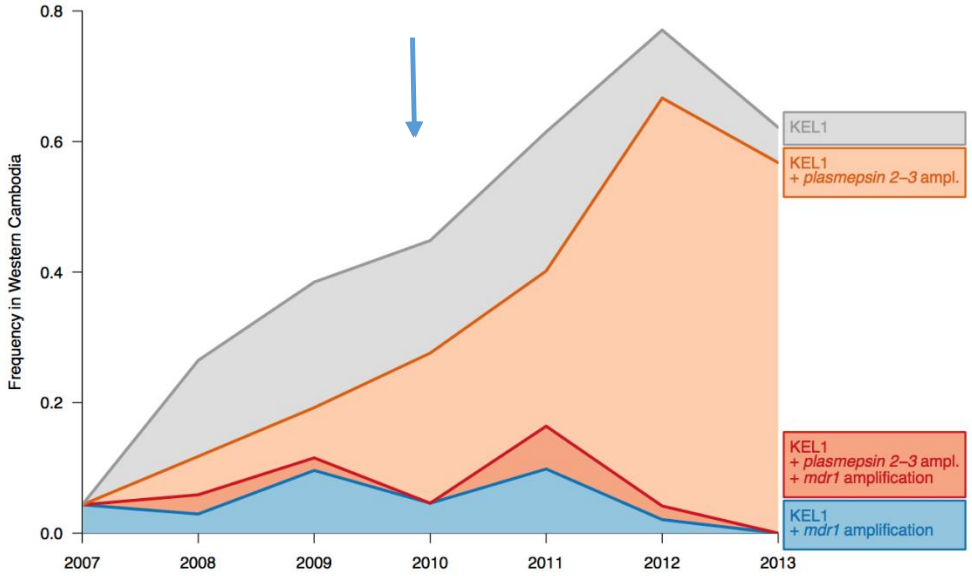
Piperaquine



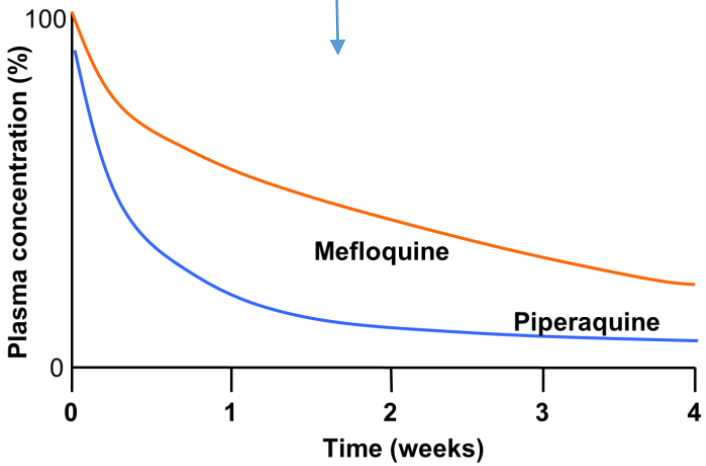
Mefloquine



Plasmepsin and MDR1 amplification mutually exclusive?



Reasonably matching PK-profiles



Amato et al. 2017

Efficacy of AL-AQ and DHA-PPQ-MQ (TRAC II trial)

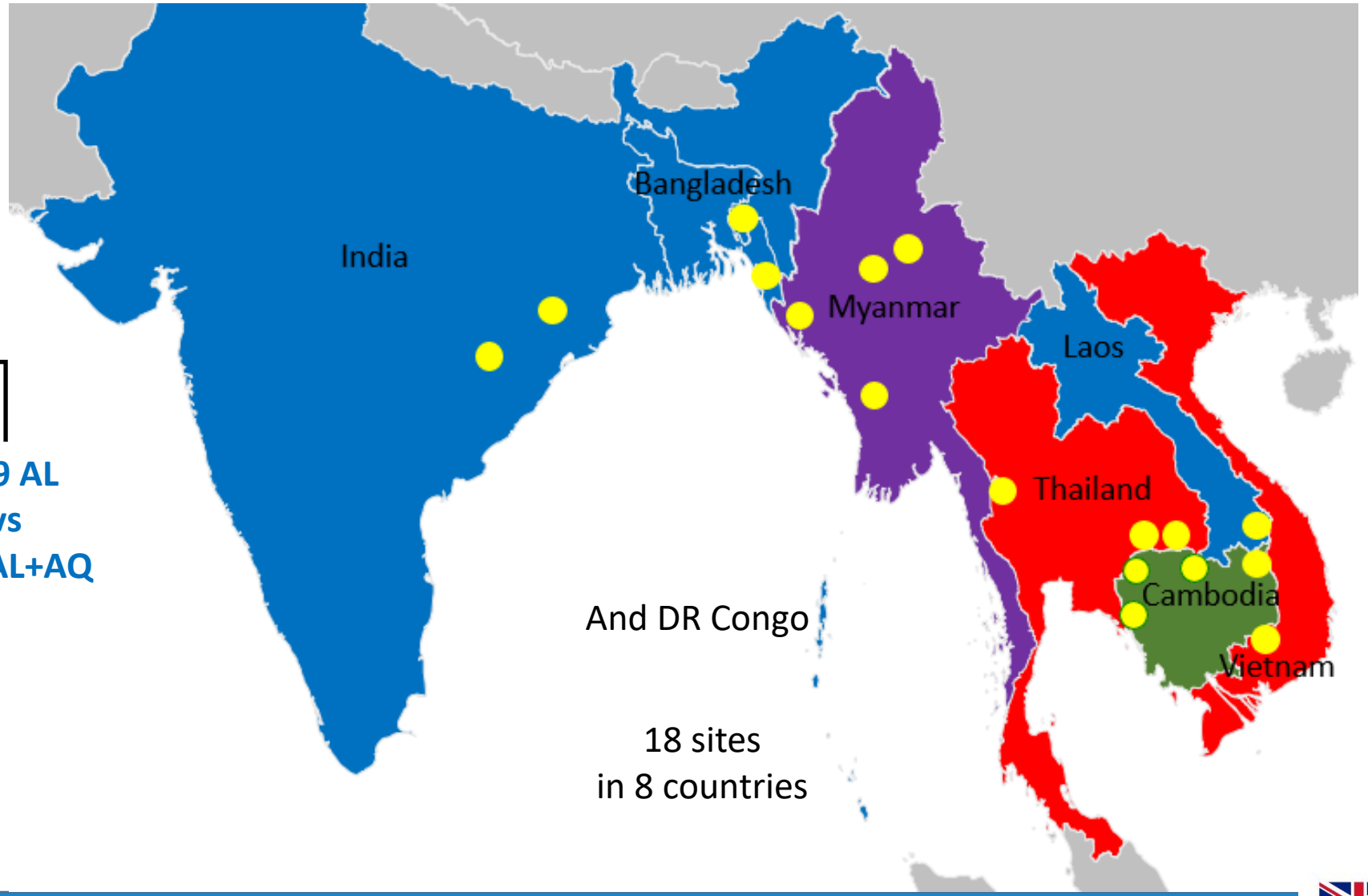
2790 assessed

1100 enrolled

183 DHA-PPQ
vs
198 DHA-PPQ-MQ

289 AL
vs
286 AL+AQ

73 AS-MQ
vs
71 DHA-PPQ-MQ



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van der Pluijm et al. *Lancet 2020*

Main results TRAC II trial

DHA-PPQ *vs* ART-MQ, DHA-PPQ+MQ

	Dihydroartemisinin–piperaquine	Dihydroartemisinin–piperaquine plus mefloquine	Artesunate–mefloquine	Risk difference	p value
Dihydroartemisinin–piperaquine *vs* dihydroartemisinin–piperaquine plus mefloquine					
Overall (n=381)	109/183 (60%; 52 to 67)	191/198 (97%; 93 to 99)	..	37% (29 to 45)	<0·0001
In Vietnam, Thailand, and Cambodia (n=293)	67/141 (48%; 39 to 56)	149/152 (98%; 94 to 100)	..	51% (42 to 59)	<0·0001
In Myanmar (n=88)	42/42 (100%; 92 to 100)	42/46 (91%; 79 to 98)	..	9% (1 to 17)	p=0·12
Artesunate–mefloquine *vs* dihydroartemisinin–piperaquine plus mefloquine (n=144)					
Overall (n=144)	..	68/71 (96%; 88 to 99)	69/73 (95%; 87 to 99)	1% (–6 to 8)	1·00

AL *vs* AL-AQ

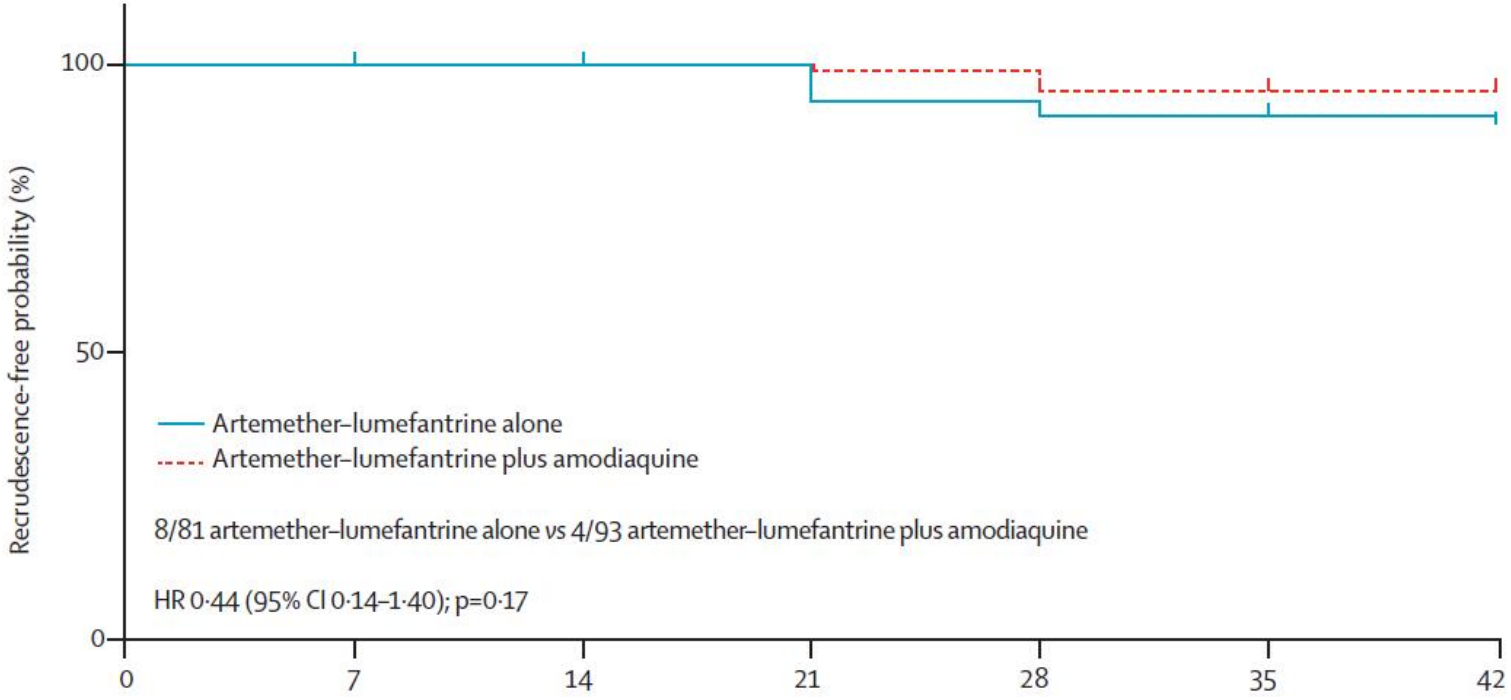
	Artemether–lumefantrine	Artemether–lumefantrine plus amodiaquine	Risk difference, %	p value
Artemether–lumefantrine *vs* artemether–lumefantrine plus amodiaquine (n=575)	279/289 (97%; 94 to 98)	281/286 (98%; 96 to 99)	2% (–1 to 4)	0·30

TRAC II trial: safety and tolerability

	Dihydroartemisinin–piperaquine group (n=183)	Dihydroartemisinin–piperaquine plus mefloquine group (n=269)	Artesunate–mefloquine group (n=73)	Artemether–lumefantrine group (n=289)	Artemether–lumefantrine plus amodiaquine group (n=286)
Vomiting within 1 h after treatment/number of treatments	8/543 (1·5%)	30/794 (3·8%)	3/219 (1·4%)	11/1721 (0·6%)	22/1703 (1·3%)
Serious adverse events	6/183 (3·3%)	10/269 (3·7%)	2/73 (2·7%)	4/289 (1·4%)	2/286 (0·7%)
Drug-related serious adverse events	4/183 (2·2%)	4/269 (1·5%)	1/73 (1·4%)	0/289 (0%)	1/286 (0·3%)
QTcB >60 ms above baseline	5/183 (2·7%)	6/269 (2·2%)	0/73 (0·0%)	1/289 (0·3%)	1/286 (0·3%)
QTcB >500 ms	0/183 (0·0%)	1/269 (0·4%)	0/73 (0·0%)	0/289 (0·0%)	0/286 (0·0%)
Bradycardia	24/183 (13·1%)	44/269 (16·4%)	9/73 (12·3%)	18/289 (6·2%)	52/286 (18·2%)

TACT-CV trial Cambodia/ Vietnam: AL vs AL+AQ

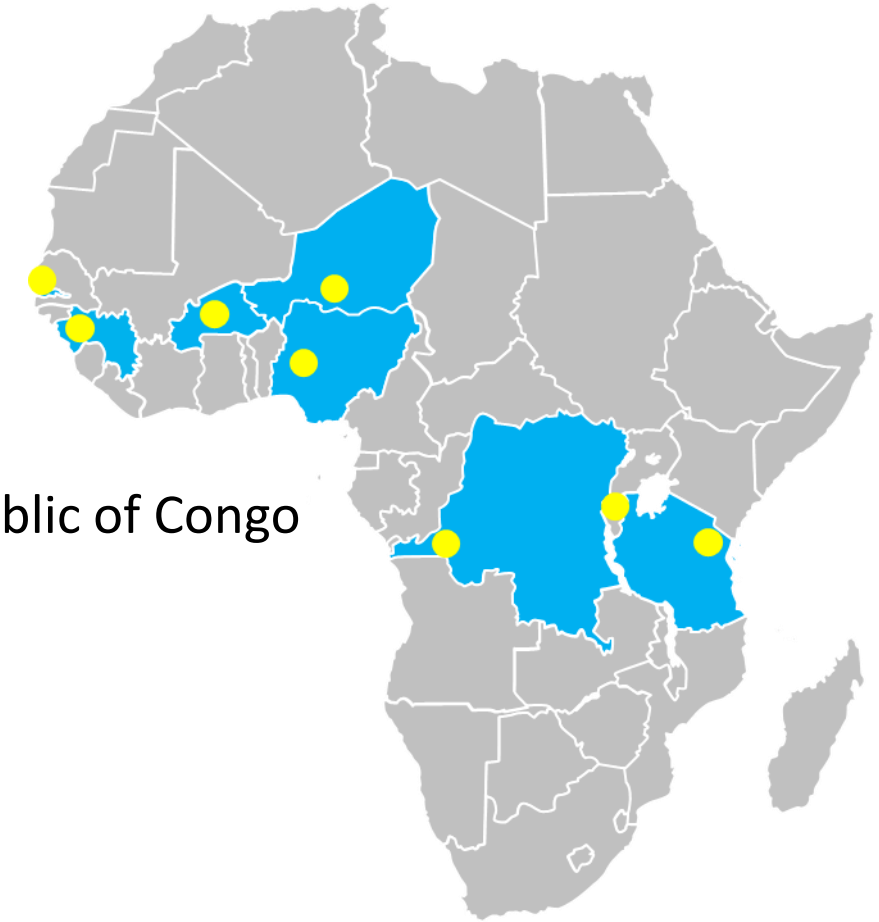
In *PfKelch* mutant infections, 42-day failure was 10% (8/81) with AL and 4% (4/93) with AL+AQ
In *PfKelch* wild-type infections there was only 1/131 (1%) recrudescence at day 42

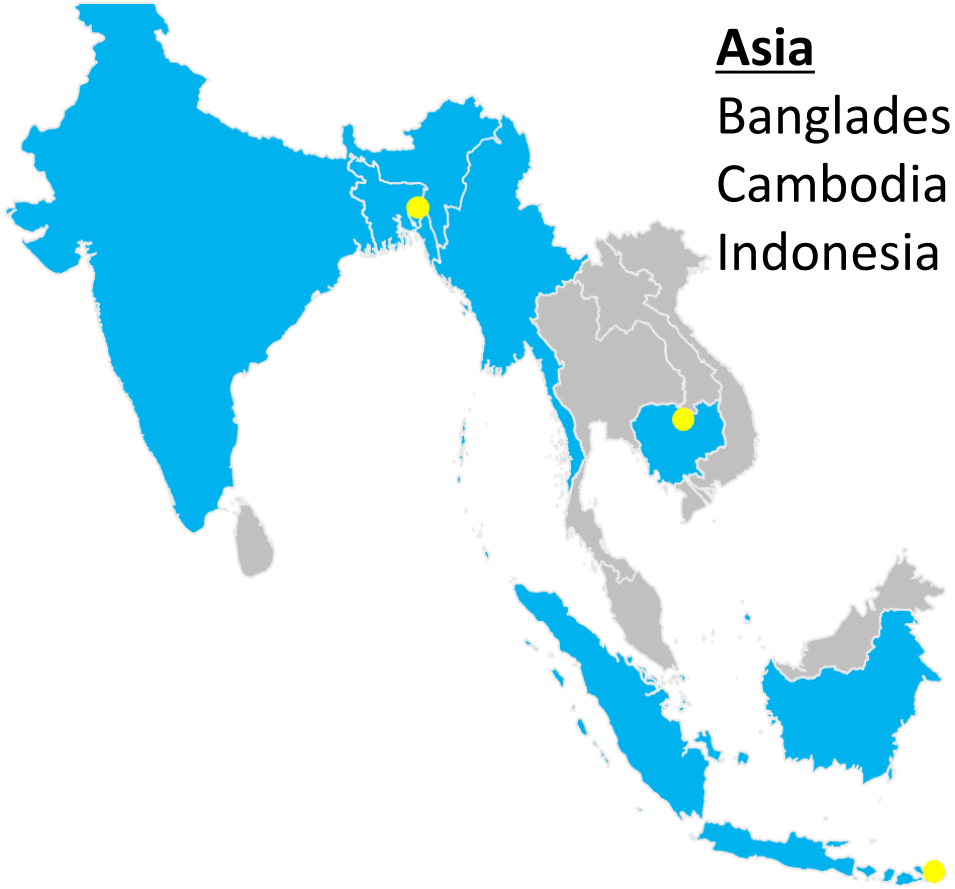


Number at risk							
Artemether–lumefantrine alone	81	81	80	79	73	68	61
Artemether–lumefantrine plus amodiaquine	93	93	92	89	88	84	81

Peto TJ et al. *Lancet Infect Dis 2022*

DeTACT: development of triple ACTs AL+AQ and AS+MQ+PPQ n=4000





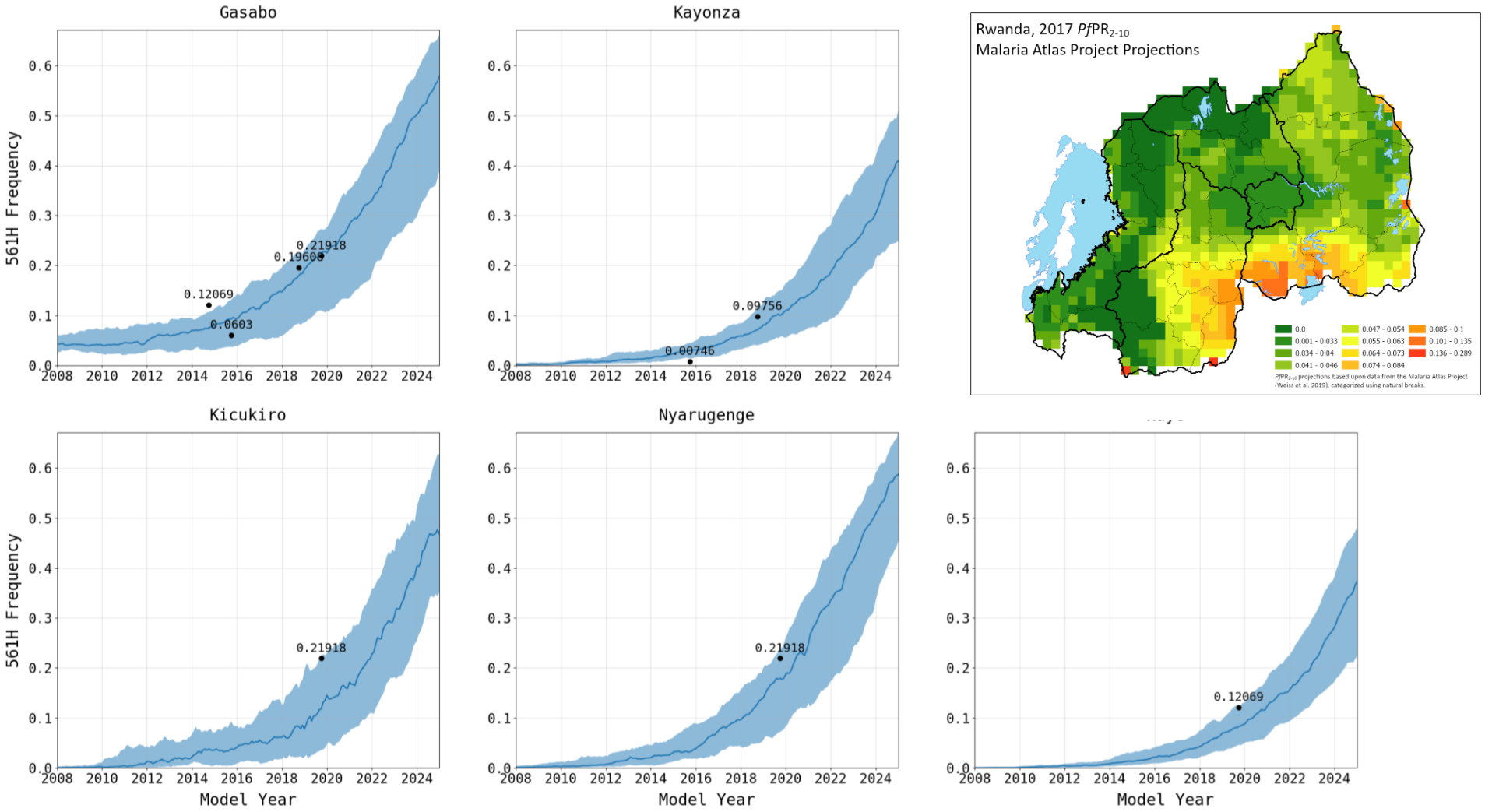
Africa

Burkina Faso
Democratic Republic of Congo
Guinea
Niger
Nigeria
Tanzania
The Gambia
Rwanda

Asia

Bangladesh
Cambodia
Indonesia

Projected trajectory of *PfKelch* 561H allele frequency in Rwanda (preliminary)



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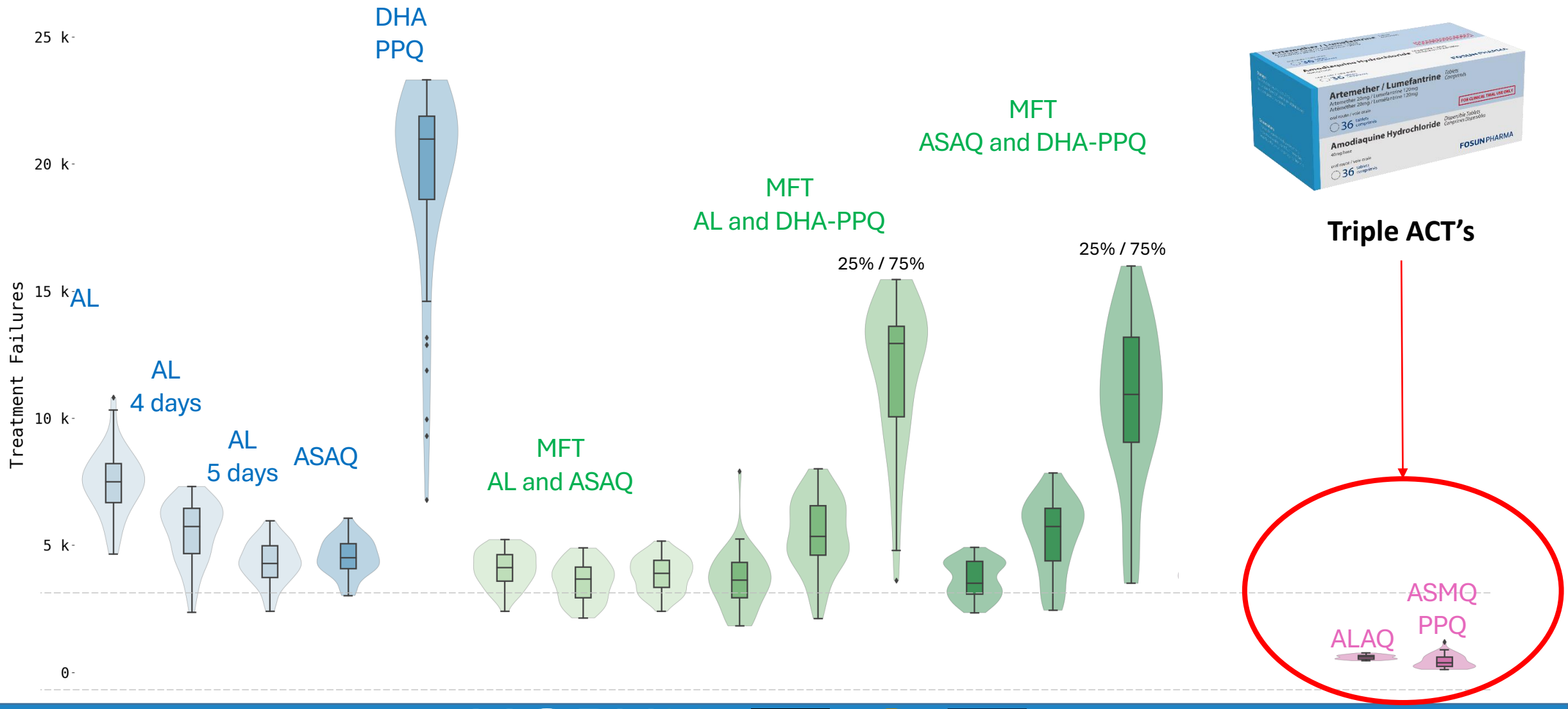
Courtesy Macej Boni & Robert Zupco

Predicted number of treatment failures in 2027 in Rwanda according to strategy (preliminary)



Courtesy Macej Boni & Robert Zupco

Exploring the market positioning of Triple ACTs

Interviews with stakeholders in Burkina Faso, Nigeria

(conducted before the reports on artemisinin resistance came out)

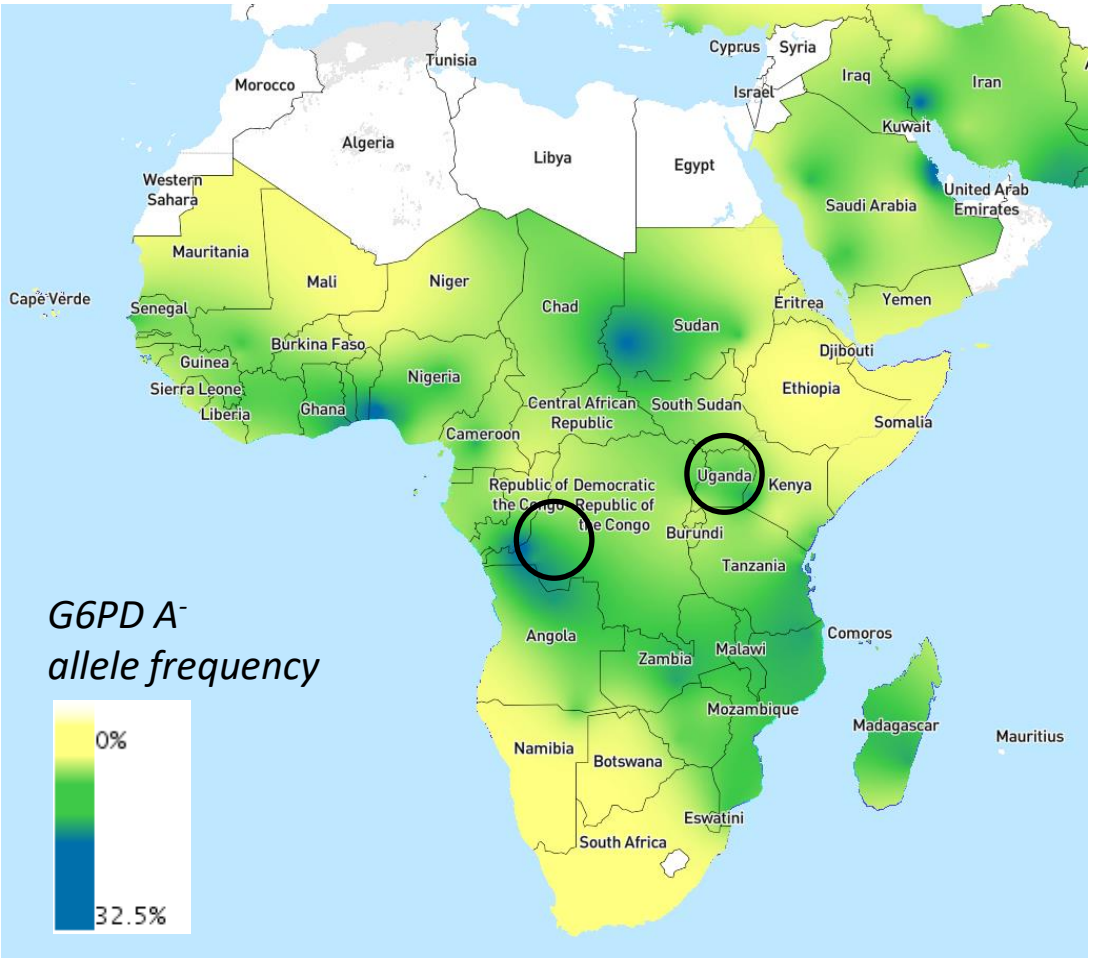
- Market prospects for TACTs largely depend on confirmation of ACT failure
- Early submission of dossiers suggested for obtaining rapid market approval
- Endorsement by WHO and funding for deployment by GFATM are enablers
- Organized implementation programs must be in place and involve all stakeholders
- Public sector distributions chains are more ready for TACTs than private sector

"I'm not too much in favor of changing as long as ACTs are still effective. So we should continue to use them until they become resistant. If it doesn't work, then we can change!" (Supplier 21, BF)

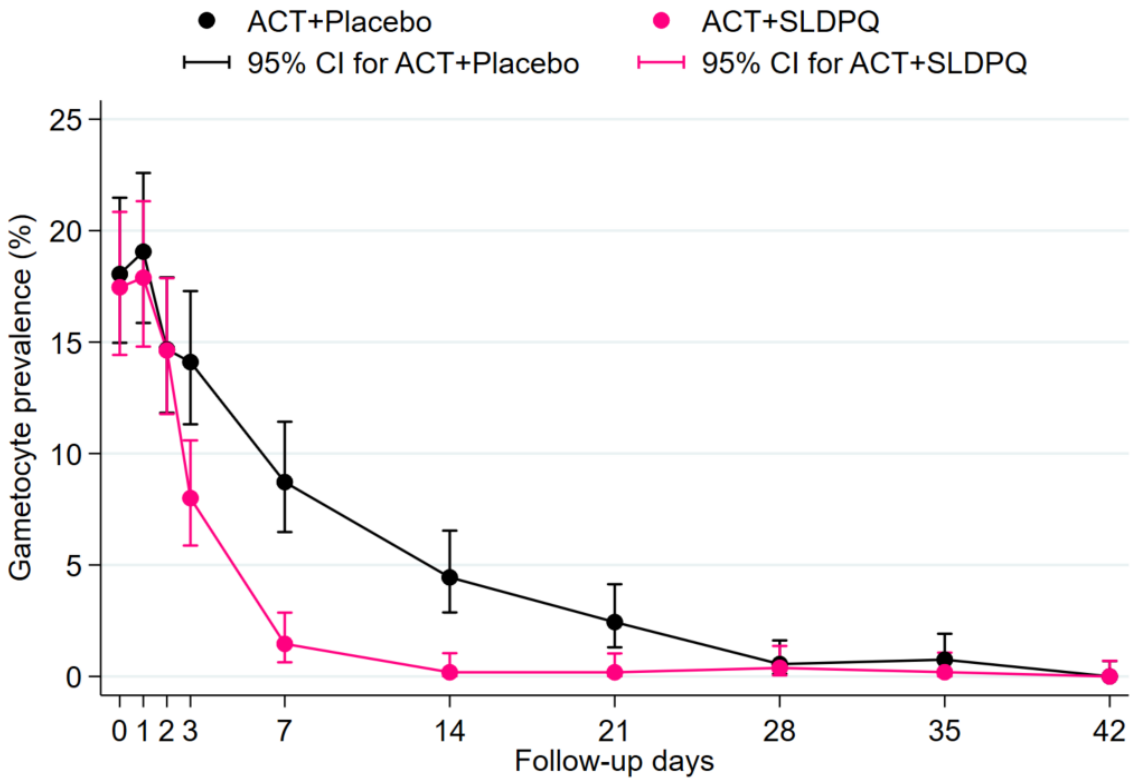
"Money is not the most important thing because what we are really interested in is the well-being of our children and ourselves" (End-user FGD 2, NG)

De Haan et al. PLoS One 2022

Safety of single low dose primaquine in African children with malaria



Randomised placebo controlled trial
Stratification according to G6PD status
n=1,137; DRC: 539, Uganda: 598



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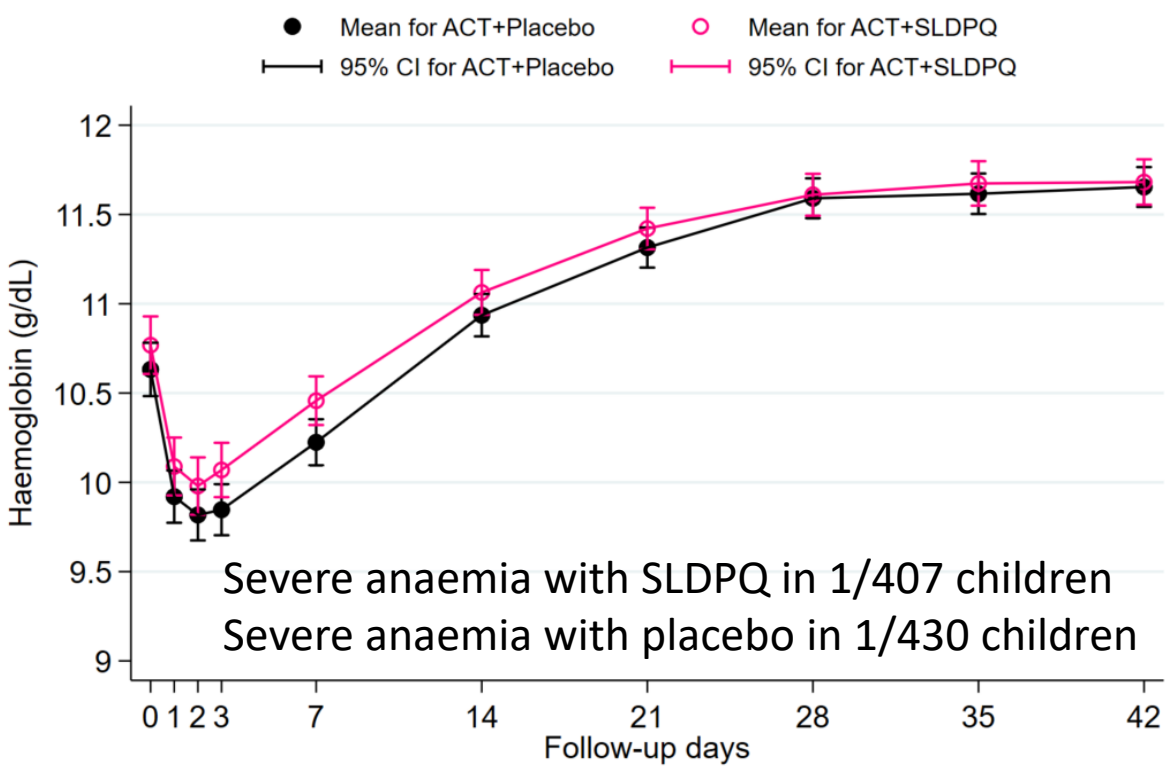
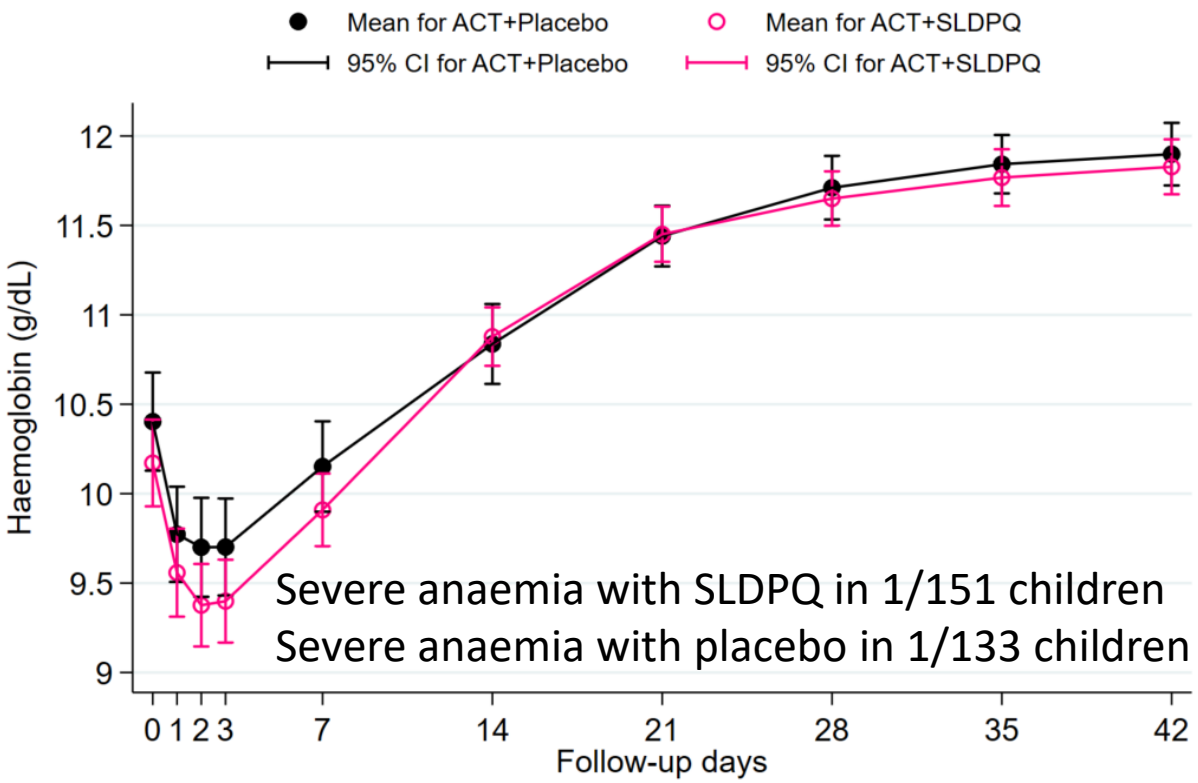
Courtesy Bob Taylor and the PAC study team

PAC study preliminary results

G6PD normal patients



G6PD deficient patients (A^-)



MORU Tropical Health Network

Courtesy Bob Taylor and the PAC study team

Summary remarks

Triple artemisinin-based therapy (AL-AQ; AS-MQ-PPQ)

- Well tolerated, no safety signals
- Efficacious, also in areas with artemisinin resistance and ACT failure
- Could delay emergence and spread of artemisinin and partner drug resistance
    - -modeling results
- -Important issue:
    - -why deploy a triple ACT when conventional ACTs are still efficacious?