

# Triple Artemisinin-based Combination Therapies (TACTs) could reduce the spread or emergence of artemisinin-resistant *Plasmodium falciparum* malaria

**DeTACT Project Investigators**

**Presenter: Mehul Dhorda, PhD**

Mahidol-Oxford Tropical Medicine Research Unit

**Roll Back Malaria Case Management Working Group Meeting**

**Kigali, 28-30 June 2022**

# Thank you!

**INSTech, Burkina Faso**

**KIMORU, DRC**

**MRC, Gambia**

**CNFRSR, Guinea**

**Epicentre, Niger**

**CEMTROD, Nigeria**

**University of Rwanda**

**NIMR-Tanga, Tanzania**

**Dev Care Foundation, Bangladesh**

**CNM, Cambodia**

**EOCRU, Indonesia**

**MORU CTSG Teams**

**MORU**  
Tropical Health Network

**University of Ghana**

**Utrecht University**

**FTM, Mahidol University**

**Tridem Pharma / Fosun**

**MMV**

**FHI Clinical**

**WWARN**

**DeTACT DSMB**

**DeTACT Project Steering Committee**



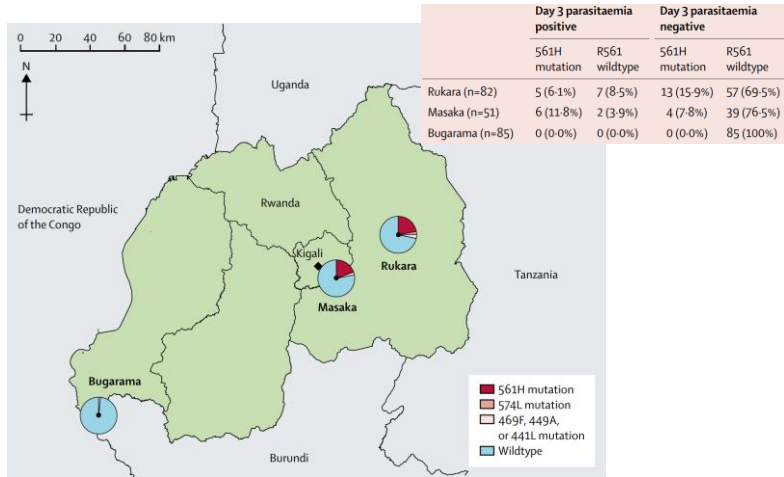
**Chanaki Amaratunga**  
DeTACT Coordinator  
MORU



**Arjen Dondorp**  
Principal Investigator  
MORU

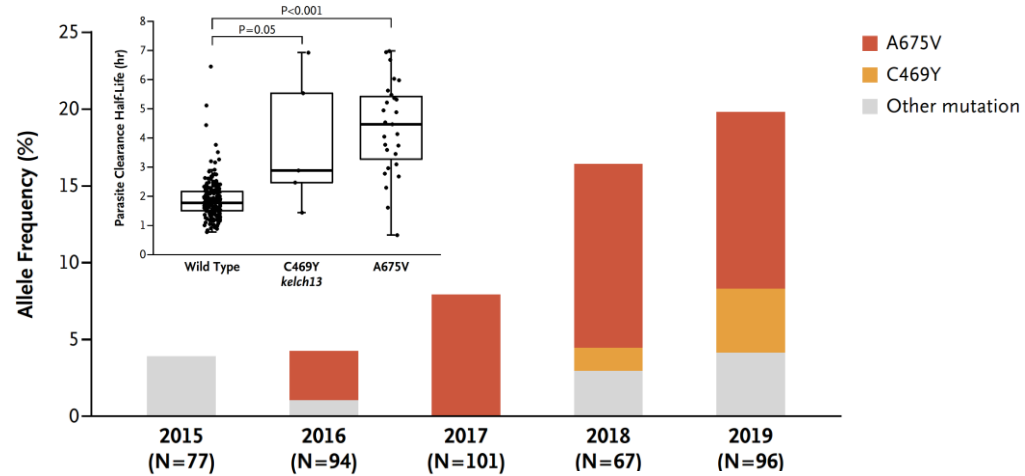
[www.tropmedres.ac](http://www.tropmedres.ac)

# Partial Artemisinin Resistance – East Africa



*Uwimana et al. LID 2021*

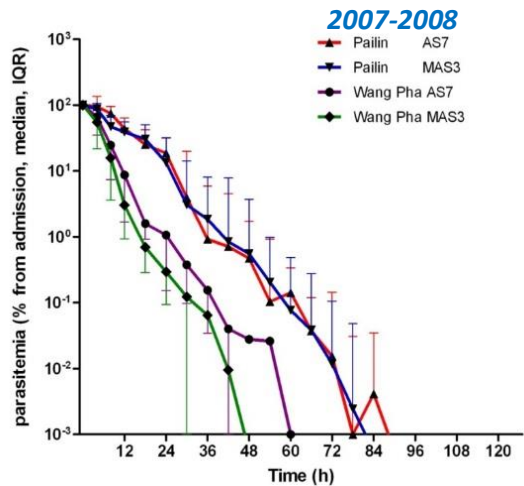
Rwanda



*Balikagala et al. NEJM 2021*

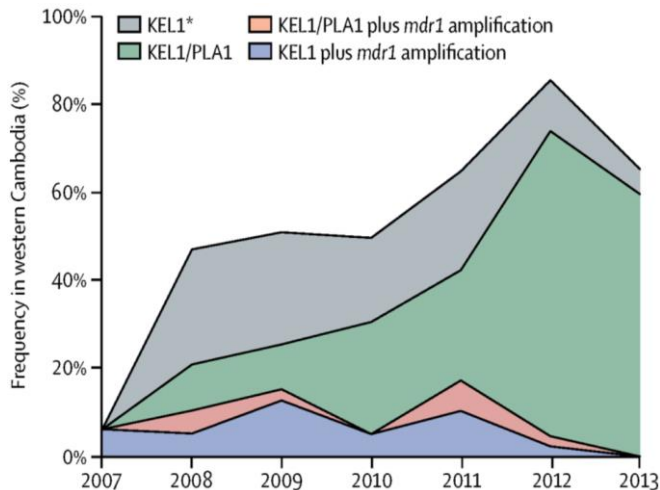
Uganda

# Partial Artemisinin Resistance – spread in GMS



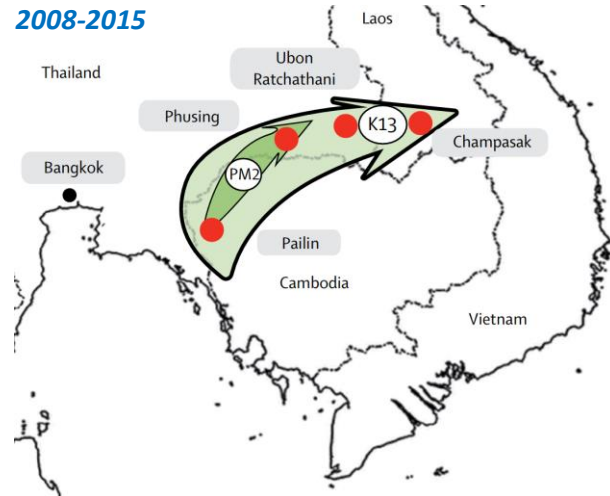
*Dondorp et al. NEJM 2009*

*Western Cambodia*



*Amato et al. Lancet ID 2018*

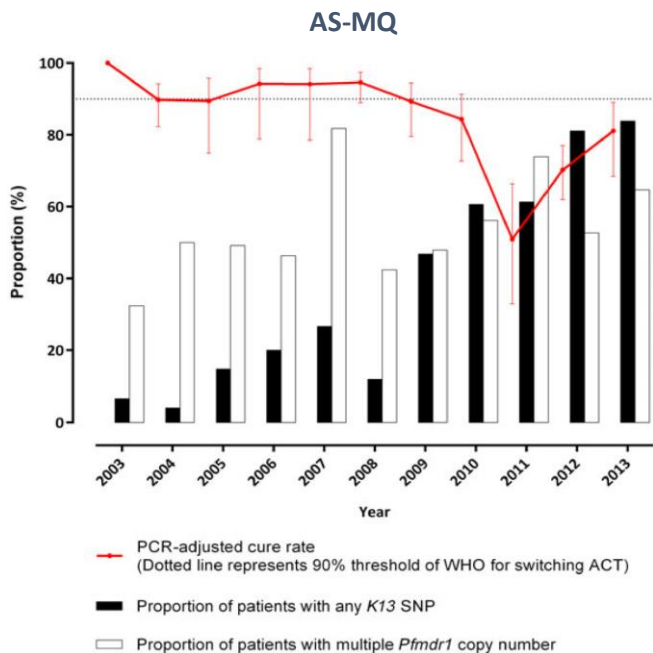
*Cambodia*



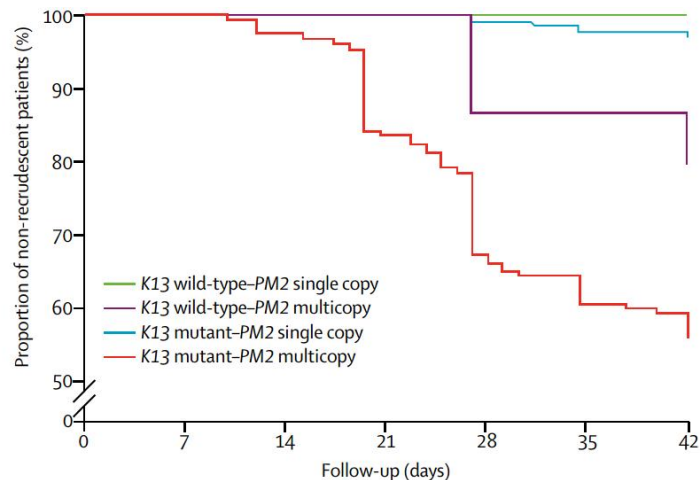
*Imwong et al. Lancet ID 2017*

*Greater Mekong Subregion*

# Partial Artemisinin Resistance $\Rightarrow \Rightarrow$ Efficacy $\downarrow$



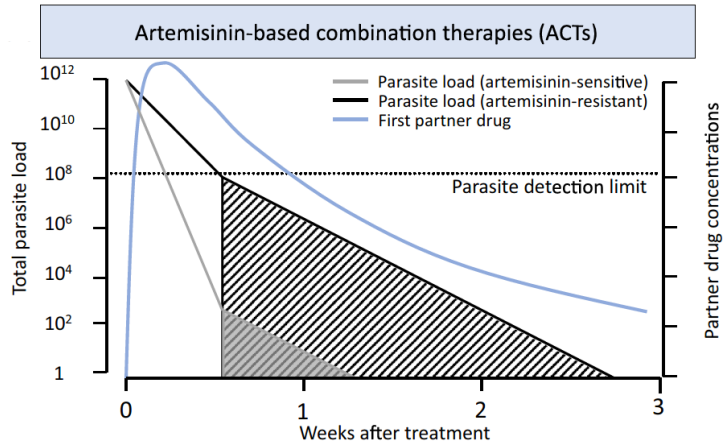
*Phyo et al. CID 2016*



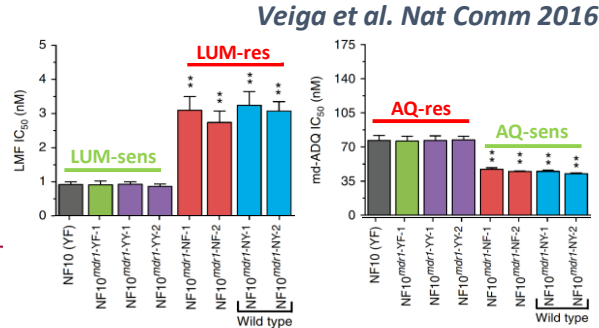
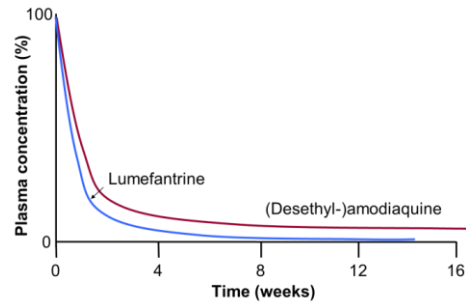
|                               | Number at risk |     |     |     |     |     |     |
|-------------------------------|----------------|-----|-----|-----|-----|-----|-----|
| K13 wild-type-PM2 single copy | 268            | 268 | 268 | 268 | 268 | 268 | 268 |
| K13 wild-type-PM2 multicopy   | 14             | 14  | 14  | 14  | 12  | 12  | 11  |
| K13 mutant-PM2 single copy    | 208            | 208 | 208 | 208 | 206 | 203 | 201 |
| K13 mutant-PM2 multicopy      | 235            | 235 | 229 | 196 | 154 | 138 | 126 |

*Witkowski et al. Lancet ID 2016*

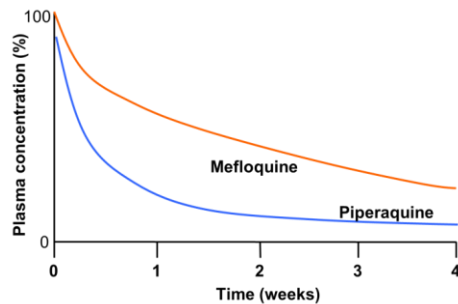
# 'Enhanced' or Triple ACTs



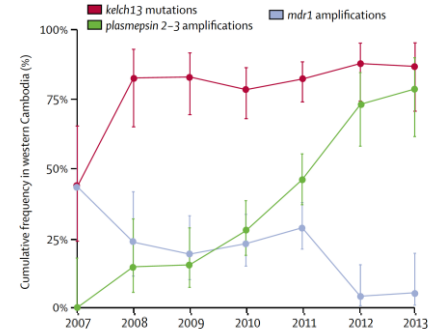
## Artemether-Lumefantrine + Amodiaquine



## Reasonably matching PK Profiles



## Counteracting resistance?



*Amato et al. LID 2018*

## Artesunate-Mefloquine + Piperaquine

# Triple ACTs – ‘TRACII’ & ‘TACT-CV’ studies



Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated *Plasmodium falciparum* malaria: a multicentre, open-label, randomised clinical trial

*van der Pluijm et al. Lancet 2020*

Triple therapy with artemether-lumefantrine plus amodiaquine versus artemether-lumefantrine alone for artemisinin-resistant, uncomplicated falciparum malaria: an open-label, randomised, multicentre trial

*Peto et al. LID 2022*



# DeTACT Project

## Development of Triple Artemisinin-based Combination Therapies

- Drug development
- **Clinical trial**
- **Mathematical modelling**
- **Bioethics**
- **Market positioning**
- Communications





# DeTACT – Bioethics and Market Studies

Phaik Yeong Cheah  
MORU



Paulina Tindana  
University of Ghana



Jean-Bosco Ouédraogo  
INSTech



Olugbenga Mokuolu  
CEMTROD



## Bioethics

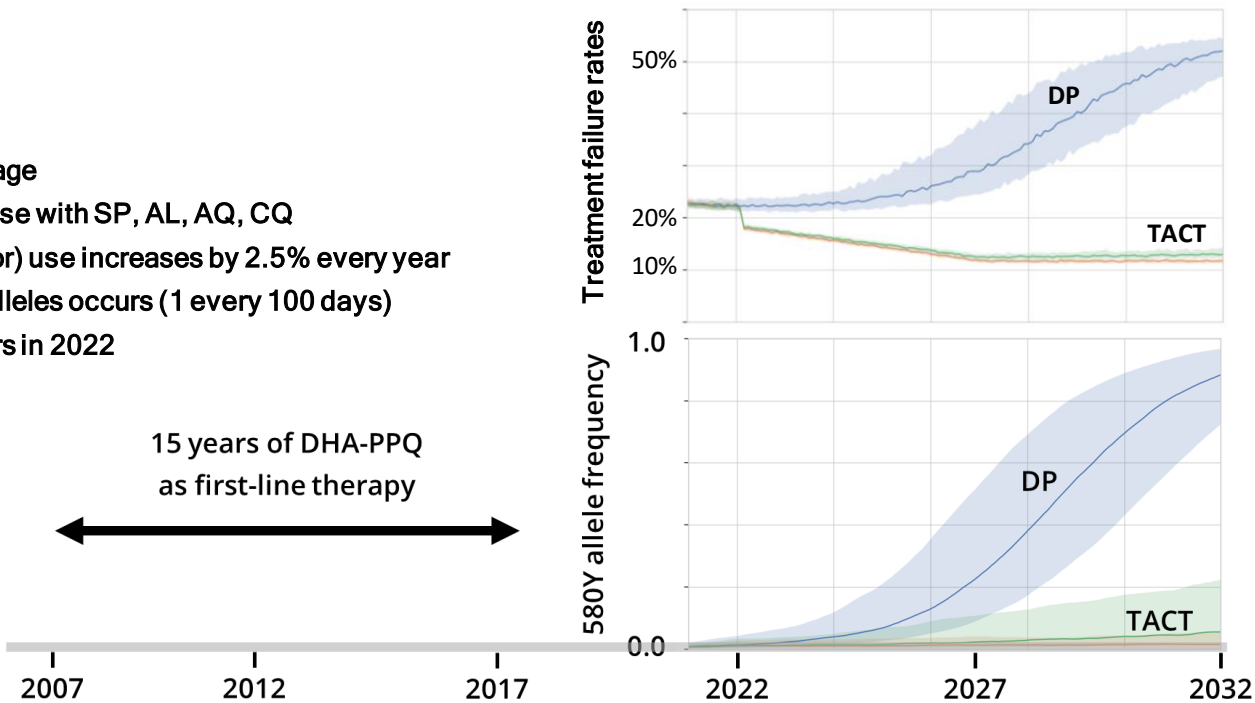
- Side-effects, burdens acceptable if minimal & mitigated
- Staggered deployment of TACTs, choice vs ACTs preferred
- Early stakeholder, community engagement will facilitate deployment

*“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)

# DeTACT – Modelling Studies

- PfPR = 1.0%
- 50% treatment coverage
- Private-market drug use with SP, AL, AQ, CQ
- First-line (public sector) use increases by 2.5% every year
- Importation of 580Y alleles occurs (1 every 100 days)
- Switch to TACT occurs in 2022



Maciej Boni  
PSU



Ricardo Aguas  
MORU

# DeTACT Trial



## Africa – 8 sites

**Burkina Faso**  
**DRC**  
**Guinea**  
**The Gambia**

**Niger**  
**Nigeria**  
**Rwanda**  
**Tanzania**

## Asia – 3 sites

**Bangladesh**  
**Cambodia**

**Indonesia**

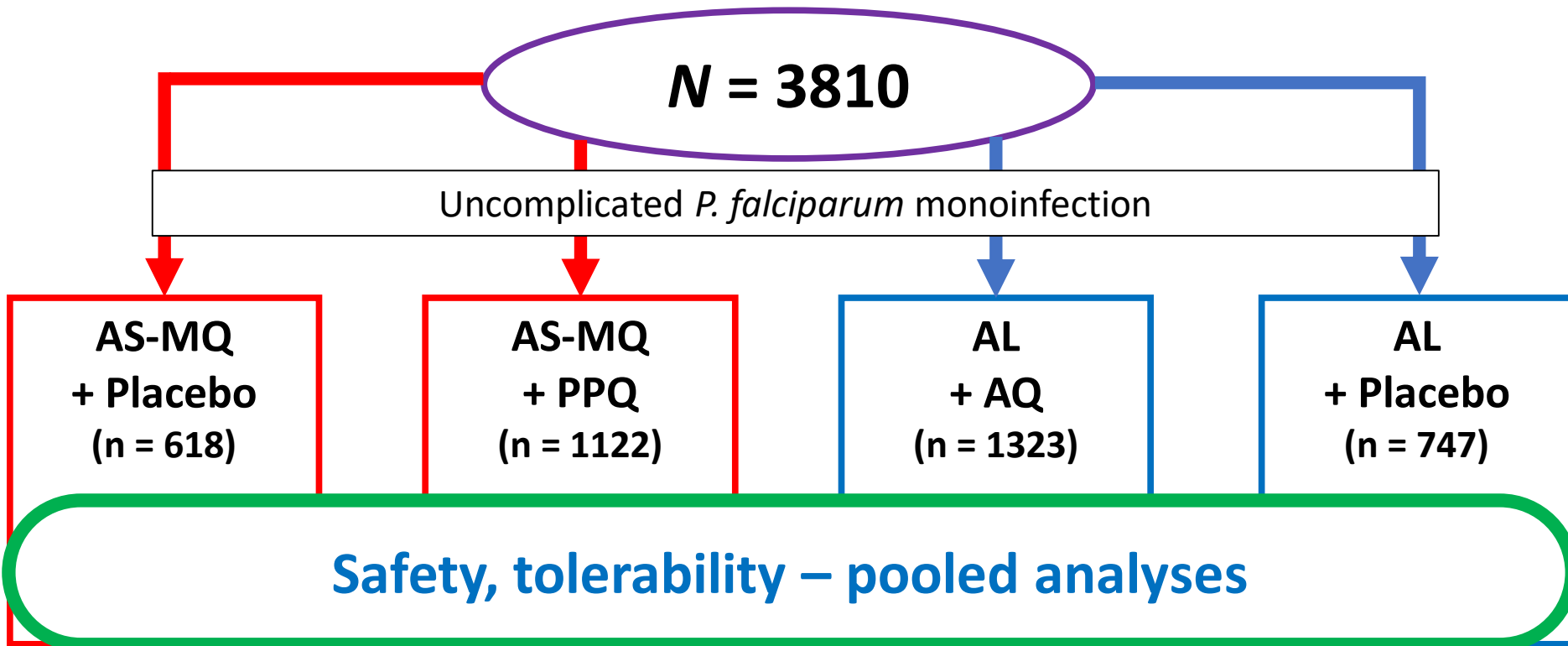
**Artemether-lumefantrine  
 + amodiaquine/placebo  
 (AL+AQ/placebo)  
 Fosun Pharma, China**

Fixed-Dose Combination in development

**Artesunate-mefloquine +  
 piperazine/placebo  
 (AS+MQ+PPQ/placebo)  
 Bilcare Research, India**

# DeTACT Trial Design

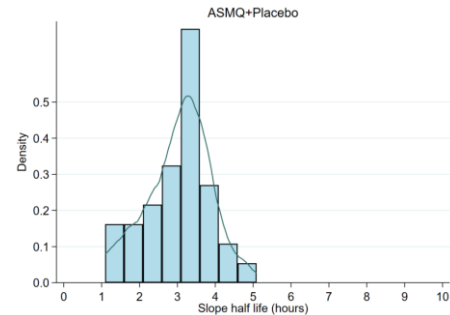
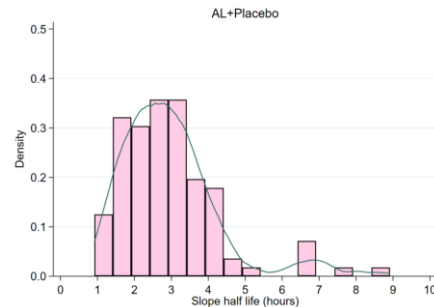
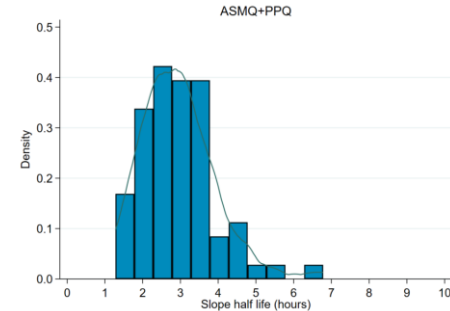
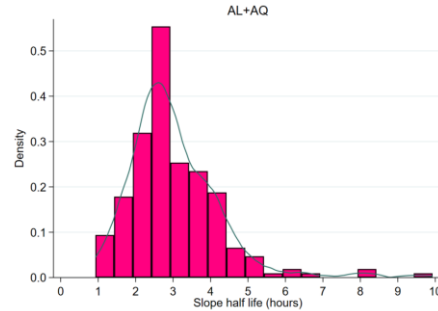
Randomised, controlled, partially blinded, non-inferiority



# DeTACT Trial – Preliminary Results (n = 500)

## Efficacy

- PCR-uncorrected efficacy similar between TACTs vs ACTs
- No signs of delayed parasite clearance outside of Cambodia



# DeTACT Trial – Safety & Tolerability (n = 500)



## Reported Symptoms

|              | AL + AQ<br>(n=250) | AL + PBO<br>(n=125) | ASMQ + PPQ<br>(n=83) | ASMQ + PBO<br>(n=42) |
|--------------|--------------------|---------------------|----------------------|----------------------|
| Grade 1-2    | 336                | 172                 | 48                   | 29                   |
| Grade 3-4    | 0                  | 0                   | 0                    | 0                    |
| <b>Total</b> | <b>336</b>         | <b>172</b>          | <b>48</b>            | <b>29</b>            |

# Triple ACTs – Summary

## AL+AQ, ASMQ+PPQ

- Well tolerated, no new safety signals
- Efficacious even with artemisinin & partner drug resistance
- Could delay emergence and spread of artemisinin & partner drug resistance (modelling results)



**MORU**   
Tropical Health Network

  
**UKaid**  
from the British people