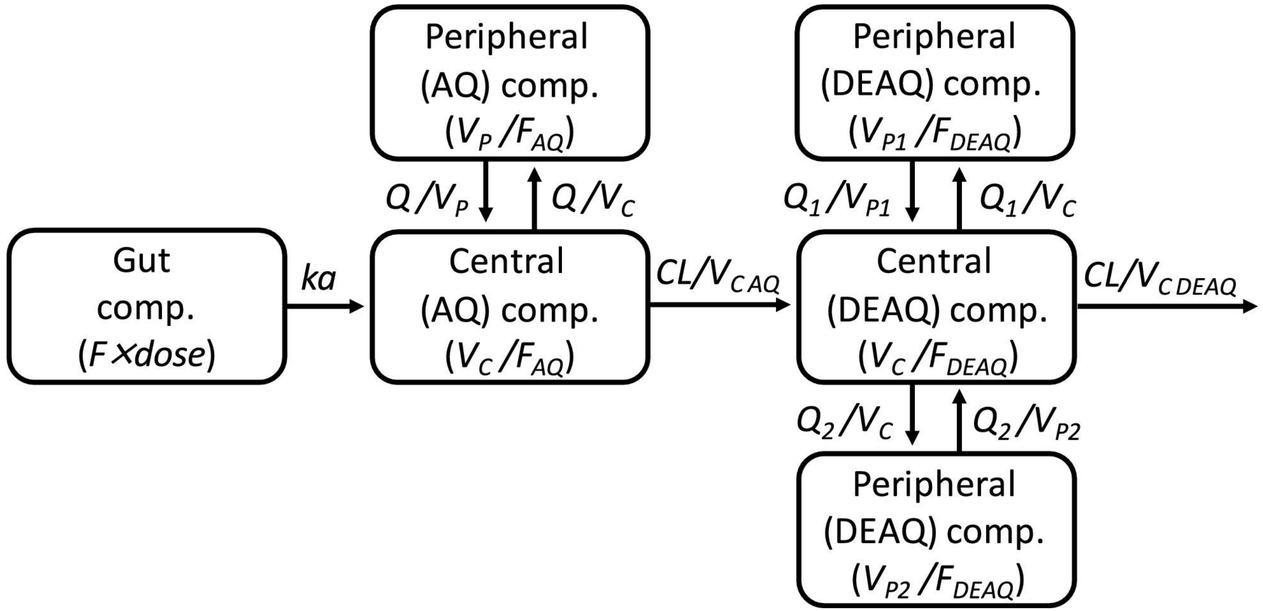
Conflict of Interest

The author has declared no conflict of interest.



Use of population pharmacokinetics to assess adherence to amodiaquine when used for seasonal malaria chemoprevention

Matthew Coldiron, Epicentre

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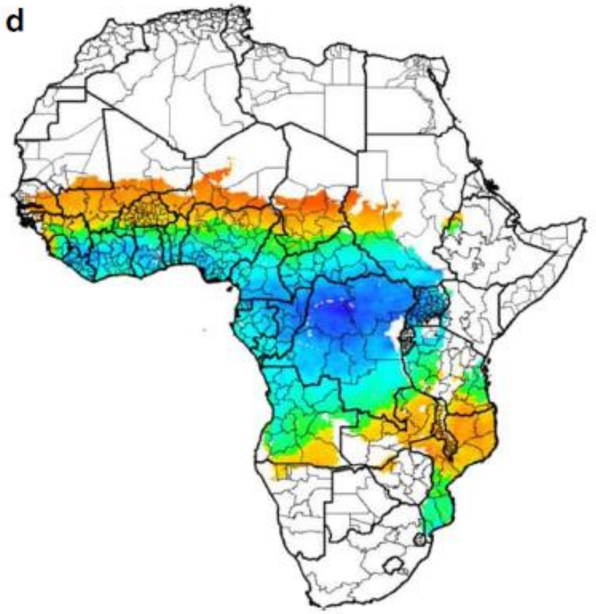
SCIENTIFIC DAYS

Seasonal malaria chemoprevention (SMC)

- Targets children aged 3-59 months in the Sahel
- Monthly treatment courses
  - **Day 1**: Sulfadoxine-pyrimethamine (SP) + amodiaquine (AQ) given by a health worker
  - **Day 2+3**: AQ given by a caregiver at home
- 3-4 months a year during rainy season
- 75% reduction in malaria incidence



Cairns, et al. *Nature Communications* (2012) 3:881.

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SCIENTIFIC DAYS

MSF and SMC

- 2013: MSF begins supporting SMC in Niger
- 2014-15: malaria incidence remains high despite SMC
- 2016: pilot of first-dose non-directly observed therapy (DOT) strategy in Magaria, Niger
- 2016: case-control study to evaluate SMC's effectiveness
  - Main results presented at MSF Scientific Days 2018
  - 85% overall protective effectiveness, but significantly lower in first-dose non-DOT areas so strategy abandoned
  - **Sub-study to evaluate adherence**

Photo : Juan Carlos Tomasi/MSF

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SCIENTIFIC DAYS

Why assess adherence?

- Poor adherence to days 2+3 of treatment course could lead to decreased protection of SMC
- Adherence to malaria <u>treatment</u> varies
  - What about <u>preventive</u> measures like SMC?
- Self-report may overestimate adherence
  - Plasma drug concentration is objective
  - Pharmacokinetics of AQ in SMC not previously described

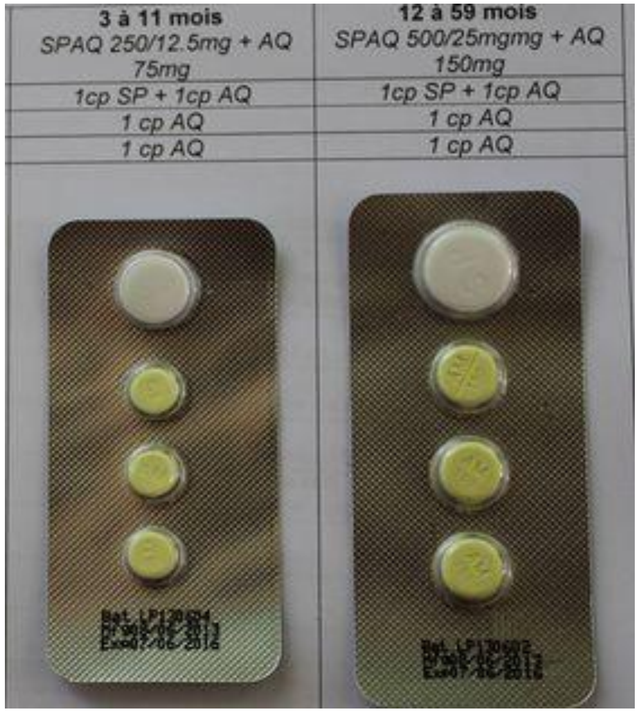

Photo : Bachir Assao

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Objectives

1. Describe the population pharmacokinetics (PK) of AQ in children receiving SMC under ideal conditions

2. Compare drug concentrations of children enrolled in case-control study to objectively assess their adherence

Field methods – population PK

- 165 children aged 3-59 months in Magaria village

- SMC doses administered at home by study nurses each day for 3 days

- Capillary blood collection
  - 0-8 hours after first dose
  - 0-6 hours after third dose
  - 6-12 hours after third dose
  - 12-24 hours after third dose
  - 4-7 days after first dose
  - 14-35 days after first dose

	B	C	D	E	F	G	H	I	J
1	Groups 1/3 start 14 Nov, groups 2/4 start 15 Nov								
2									
3	ID	Menage	Group	Date of first dose	Second dose	Third dose	Prelevement 1	Prelevement 2	Prelevement 3
118	115	M095	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 11:00	11/17/16 17:00	11/22/16 17:00
119	116	M095	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 11:00	11/17/16 17:00	11/22/16 17:00
120	117	M096	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 11:00	11/17/16 16:00	11/21/16 17:00
121	118	M097	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 13:00	11/17/16 18:00	11/21/16 15:00
122	119	M097	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 13:00	11/17/16 18:00	11/21/16 15:00
123	120	M097	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 13:00	11/17/16 18:00	11/21/16 15:00
124	121	M098	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 14:00	11/17/16 16:00	11/22/16 15:00
125	122	M098	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 14:00	11/17/16 16:00	11/22/16 15:00
126	123	M098	2	11/15/16 7:00	11/16/16 7:00	11/17/16 7:00	11/15/16 14:00	11/17/16 16:00	11/22/16 15:00
127	124	M124	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 16:00	11/18/16 7:00	12/10/16 7:00
128	125	M125	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 16:00	11/18/16 7:00	12/10/16 7:00
129	126	M126	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 17:00	11/18/16 7:00	12/10/16 17:00
130	127	M126	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 17:00	11/18/16 7:00	12/10/16 17:00
131	128	M127	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 17:00	11/18/16 7:00	12/11/16 7:00
132	132	M128	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 18:00	11/18/16 11:00	12/11/16 7:00
133	129	M128	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 18:00	11/18/16 11:00	12/11/16 7:00
134	130	M128	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 18:00	11/18/16 11:00	12/11/16 17:00
135	131	M128	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 18:00	11/18/16 11:00	12/11/16 17:00
136	133	M129	4	11/15/16 13:00	11/16/16 13:00	11/17/16 13:00	11/17/16 18:00	11/18/16 9:00	12/12/16 17:00

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Ethics committee approvals
CCNE Niger 14/2016/CCNE
MSF-ERB 1624

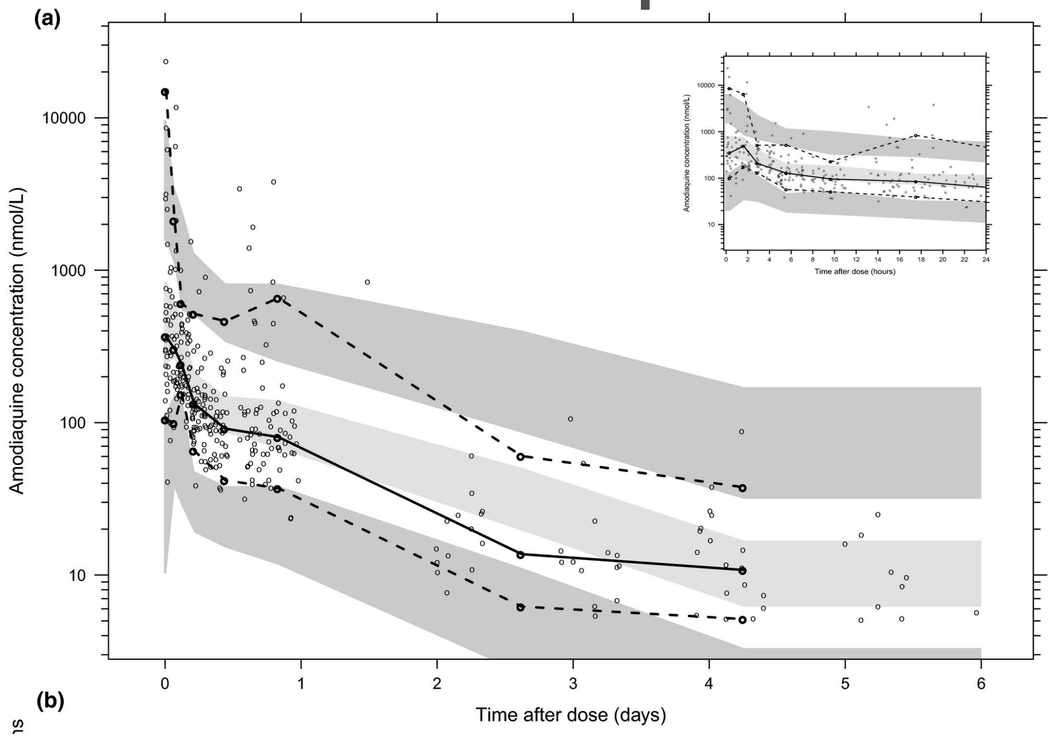
SCIENTIFIC DAYS

Lab methods – population PK

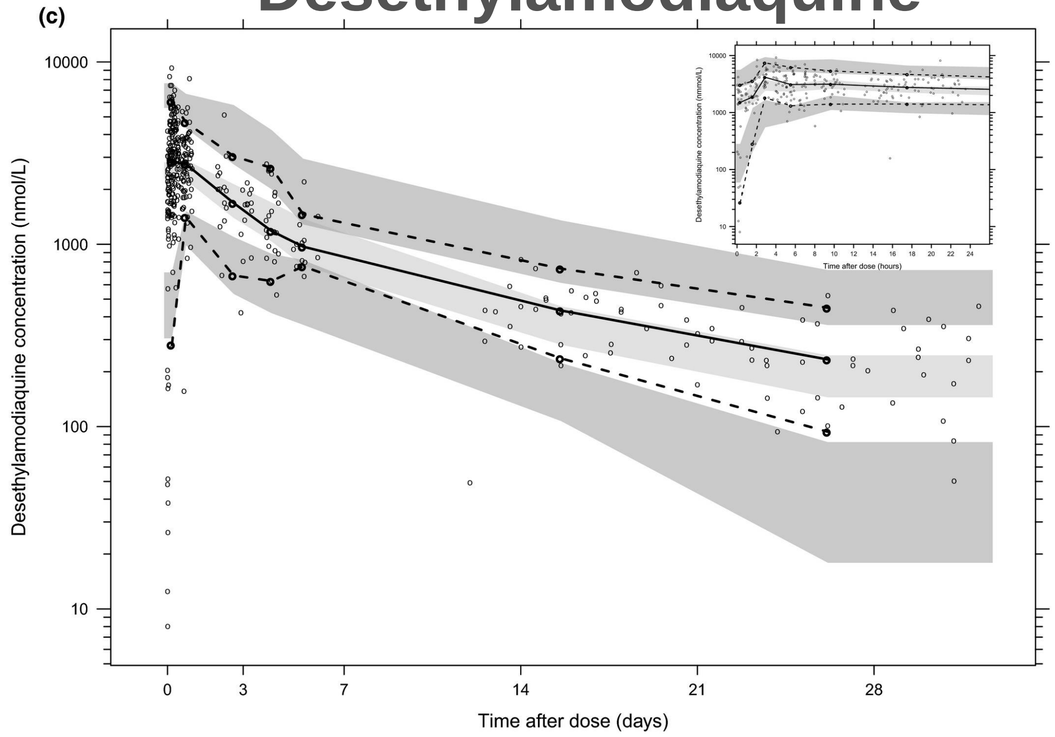
- Joel Tarning's lab at Mahidol-Oxford Tropical Medicine Research Unit
- Concentrations of AQ and desethylamodiaquine (DEAQ) determined using liquid chromatography tandem mass spectrometry-based assay
- Concentration-time data evaluated simultaneously using nonlinear mixed-effects modelling
- Sensitivity and specificity of different cut-off thresholds evaluated
  - Basis for assessment of adherence in case-control population

Results – population PK

Amodiaquine



Desethylamodiaquine



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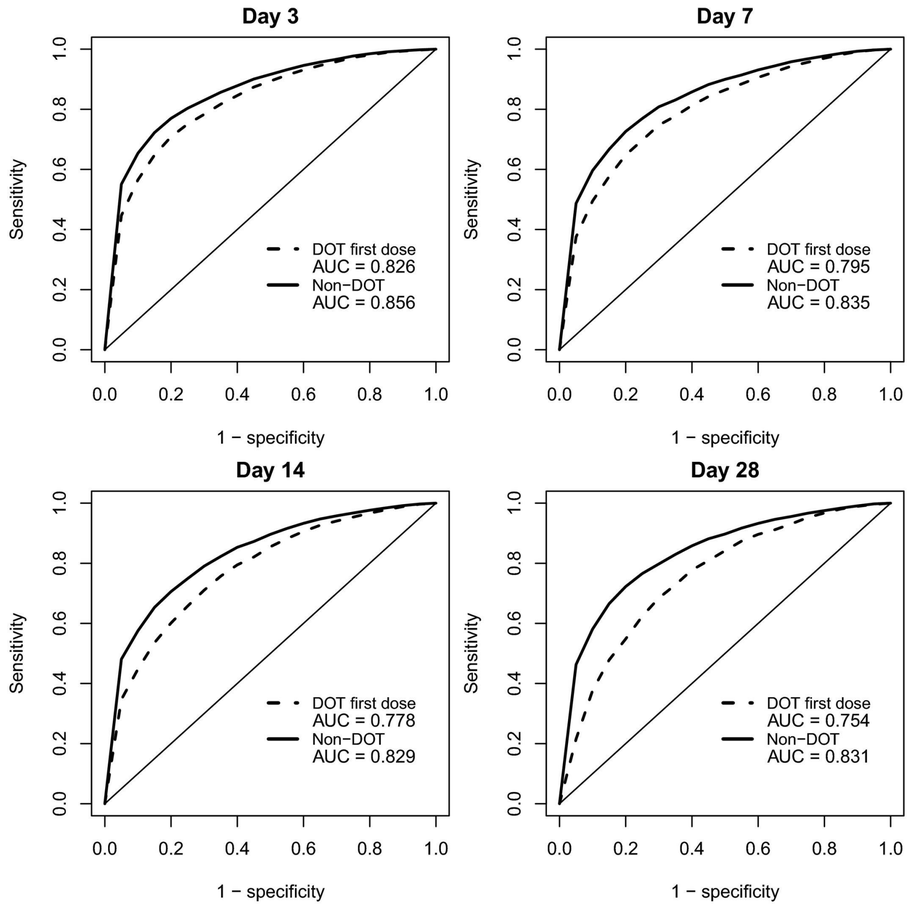
Ding et al. Clin Pharmacol Ther. 2020;107(5):1179-1188.
doi: 10.1002/cpt.1707

SCIENTIFIC DAYS

Results – cut-off thresholds



- Good discriminating capacity: area under the curve (AUC) >0.75 at all time points
- Thresholds between 20th and 30th percentiles had best overall performance
  - Sensitivity: 65-77%
  - Specificity: 70-80%
- Most conservative threshold of 5th percentile had 95% specificity

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SCIENTIFIC DAYS

Results – correct adherence

	5th percentile cut-off	Optimal percentile cut-off
Controls		
First-dose DOT (n=327)	55 (17%)	27 (8%)
First-dose non-DOT (n=349)	61 (18%)	29 (8%)
Cases		
First-dose DOT (n=84)	8 (10%)	6 (7%)
First-dose non-DOT (n=109)	5 (5%)	3 (3%)

Ding et al. Clin Pharmacol Ther. 2020;107(5):1179-1188.
doi: 10.1002/cpt.1707

Conclusions

- First description of the population PK of AQ when administered as part of SMC
  - Robust model with good predictive performance
- Limitations
  - Convenience sampling was used for population PK cohort
  - Single-site study
- Poor adherence to 3-day course of AQ during SMC
  - Possible explanations: medicine hoarding, SMC fatigue, spitting/vomiting, giving to older children not targeted by SMC, etc.
- Effectiveness of SMC was high despite poor adherence to AQ
  - Suggests that benefit was largely due to single-dose SP
- Poor adherence to AQ may lead to resistance of both AQ and SP

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SCIENTIFIC DAYS

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