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# The “Development of Triple Artemisinin-based Combination Therapies (DeTACT)” project

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DeTACT principal investigator: Arjen Dondorp (Arjen@tropmedres.ac)

**DeTACT project coordinator: Chanaki Amaratunga** (chanaki@tropmedres.ac)

DeTACT-Africa coordinator: Mehul Dhorda (mehul@tropmedres.ac)



RBM CRSPC Meeting  
Kampala, Uganda – 03-06 Oct 2023



# Artemisinin-based Combination Therapy (ACT)



Artemether-lumefantrine

Artesunate-mefloquine

Dihydroartemisinin-piperaquine

Artesunate-amodiaquine

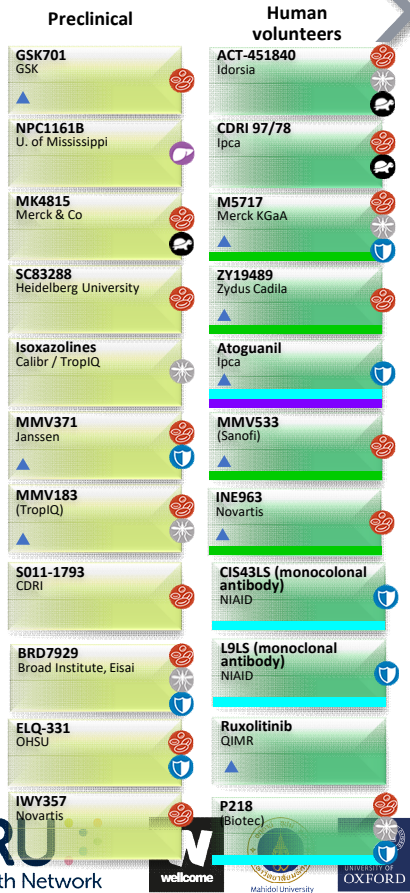
Artesunate-sulphadoxine-pyrimethamine

Artesunate-pyronaridine

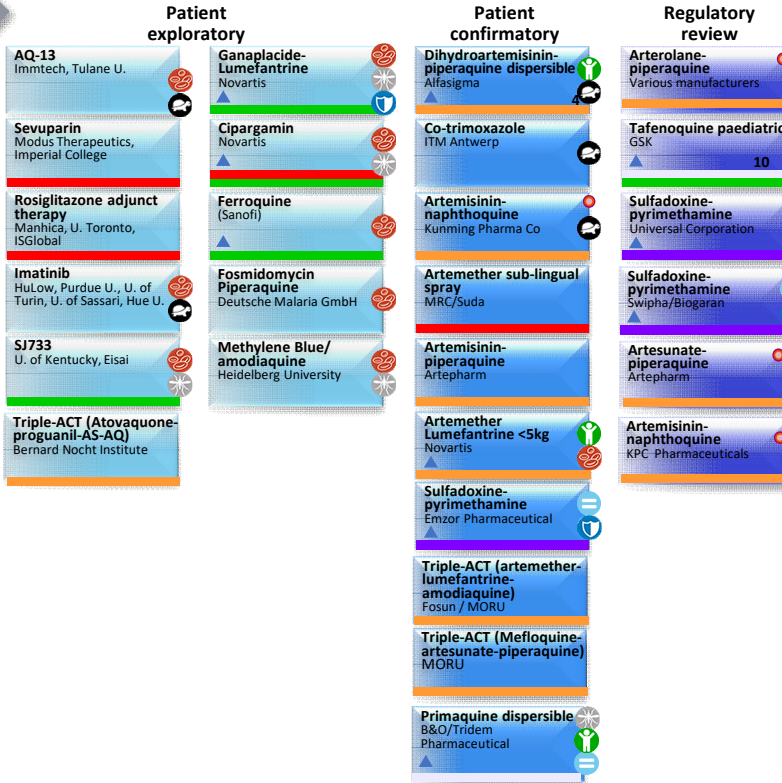


# Global Portfolio of Antimalarial Medicines

## Translational



## Product development



## Access



MMV support to projects may include financial, in-kind, and advisory activities.

Footnotes: Included in MMV portfolio after product approval and/or development. DNDi and partners completed development and registration of ASMQ and ASAQ. Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing. WHO Prequalified OR approved/positive opinion by regulatory bodies who are ICH members/observers. paediatric formulation. via a bioequivalence study. Past partners are in brackets (-).

# Artemisinin resistance presents as slower clearance

The NEW ENGLAND JOURNAL of MEDICINE

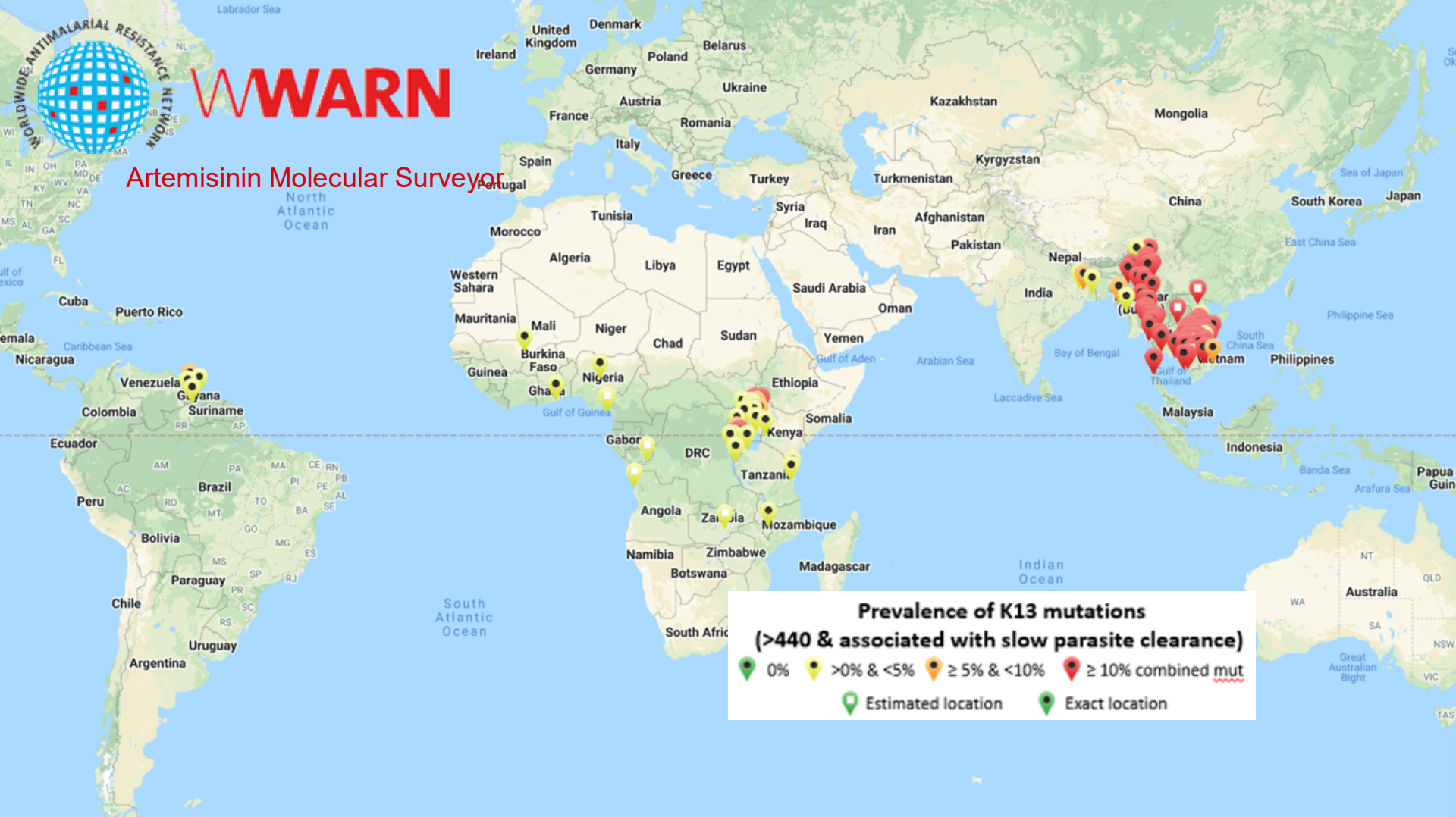
ORIGINAL ARTICLE

## Artemisinin Resistance in *Plasmodium falciparum* Malaria

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D.,  
Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D.,  
Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hanpithakpong, Ph.D.,  
Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D.,  
Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharath Lim, M.D.,  
Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D.,  
Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D.,  
Duong Socheat, M.D., and Nicholas J. White, F.R.S.



## Artemisinin Molecular Surveyor

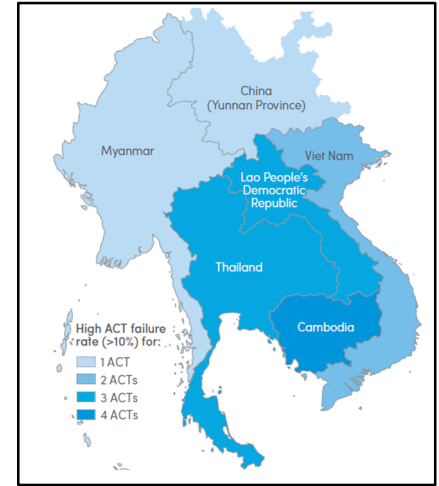
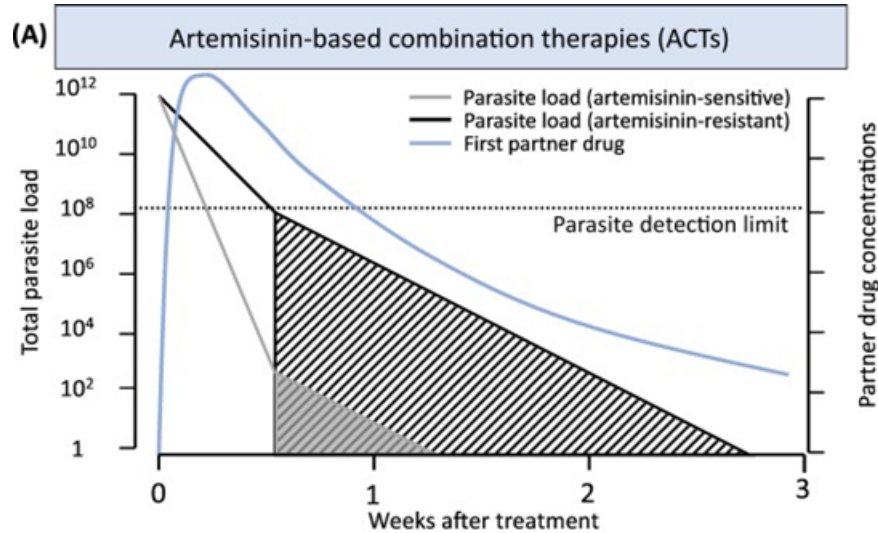
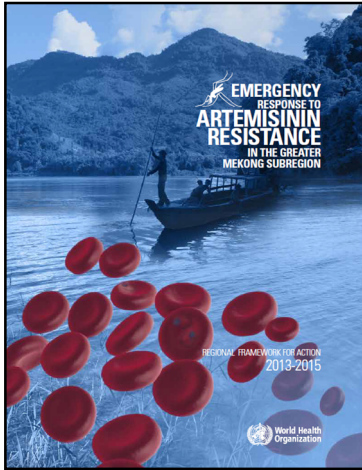


**Prevalence of K13 mutations  
(>440 & associated with slow parasite clearance)**

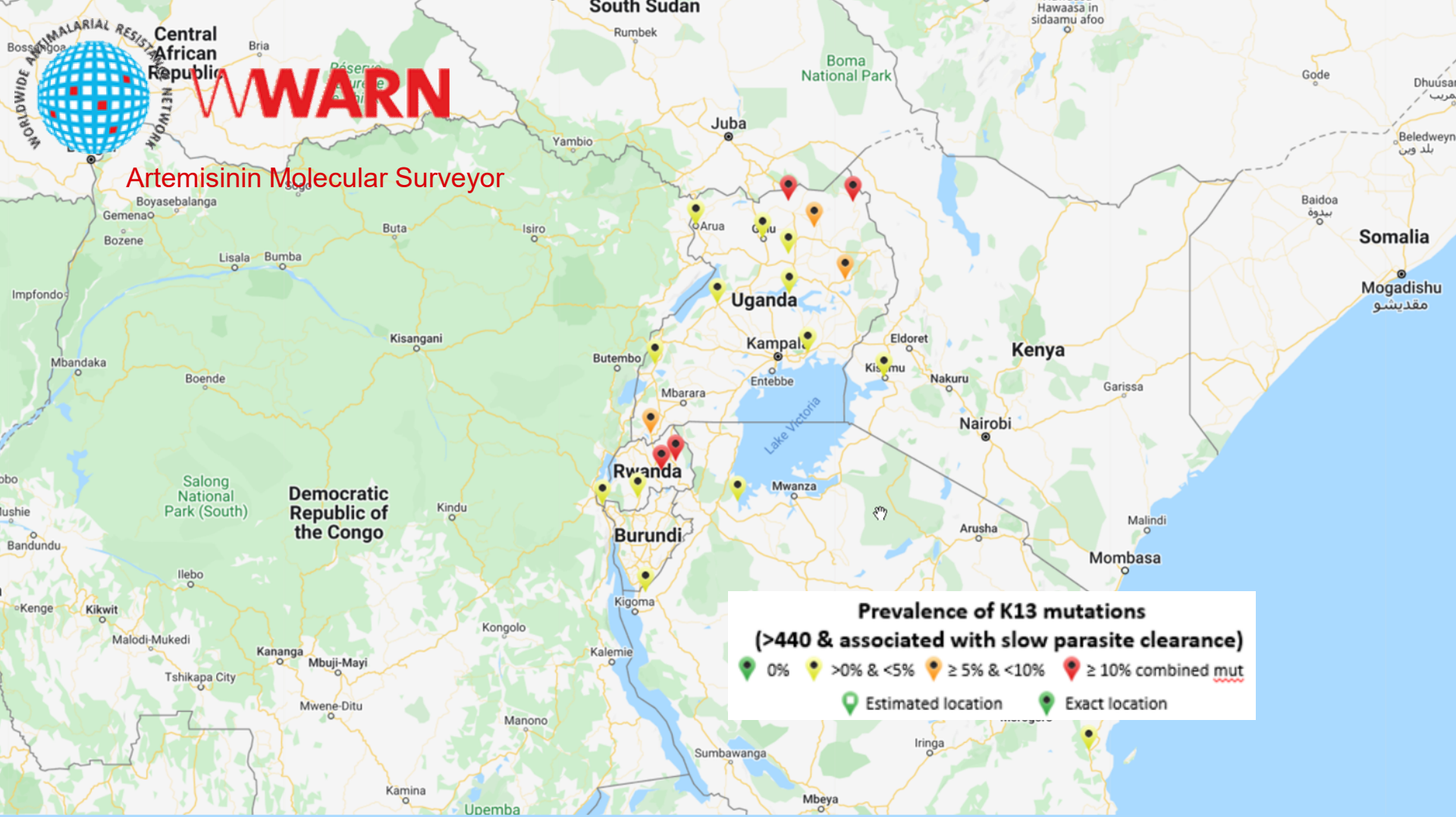
- 0%
- >0% & <5%
- ≥ 5% & <10%
- ≥ 10% combined mut

Estimated location      Exact location

# ACTs are failing in Southeast Asia



**Global spread of multidrug-resistant parasites could derail malaria elimination efforts and reverse all recent gains in malaria control**



# Artemisinin resistance in Africa

## LETTERS

<https://doi.org/10.1038/s41591-020-1005-2>

nature  
medicine



### OPEN

## Emergence and clonal expansion of in vitro artemisinin-resistant *Plasmodium falciparum* kelch13 R561H mutant parasites in Rwanda

Aline Uwimana<sup>1,15</sup>✉, Eric Legrand<sup>2,15</sup>, Barbara H. Stokes<sup>3</sup>, Jean-Louis Mangala Ndikumana<sup>1</sup>, Marian Warsame<sup>4</sup>, Noella Umulisa<sup>5,6</sup>, Daniel Ngamije<sup>7</sup>, Tharcisse Munyaneza<sup>8</sup>, Jean-Baptiste Mazarati<sup>9</sup>, Kaendi Munguti<sup>9</sup>, Pascal Campagne<sup>10</sup>, Alexis Criscuolo<sup>10</sup>, Frédéric Arley<sup>11</sup>, Monique Murindahabi<sup>12</sup>, Pascal Ringwald<sup>13</sup>, David A. Fidock<sup>3,14</sup>, Aimable Mbituyumuremyi<sup>1</sup> and Didier Menard<sup>2</sup>✉

## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 23, 2021

VOL. 385 NO. 13

### Evidence of Artemisinin-Resistant Malaria in Africa

Betty Balikagala, M.D., Ph.D., Naoyuki Fukuda, M.D., D.T.M.H., Ph.D., Mie Ikeda, Ph.D., Osbert T. Katuro, B.Sc., Shin-Ichiro Tachibana, Ph.D., Masato Yamauchi, M.P.H., Ph.D., Walter Opio, M.D., Sakurako Emoto, M.D., Denis A. Anywar, M.Sc., Eisaku Kimura, M.D., Ph.D., Nirianne M.Q. Palacpac, Ph.D., Emmanuel I. Odongo-Aginya, Ph.D., Martin Ogwang, M.D., M.M.E.D., Toshihiro Horii, Ph.D., and Toshihiro Mita, M.D., Ph.D.

## nature microbiology



### Analysis

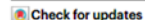
<https://doi.org/10.1038/s41564-023-01461-4>

## *Plasmodium falciparum* resistant to artemisinin and diagnostics have emerged in Ethiopia

Received: 6 March 2023

Accepted: 26 July 2023

Published online: 28 August 2023



Abebe A. Fola<sup>1,2,9</sup>, Sindew M. Feleke<sup>3,9</sup>, Hussein Mohammed<sup>3</sup>, Bokretson G. Brhane<sup>3</sup>, Christopher M. Hennelly<sup>4</sup>, Ashenafi Assefa<sup>5,4</sup>, Rebecca M. Crudal<sup>1,2</sup>, Emily Reichert<sup>6</sup>, Jonathan J. Juliano<sup>6</sup>, Jane Cunningham<sup>6</sup>, Hassen Mamo<sup>7</sup>, Hiwot Solomon<sup>8</sup>, Geremew Tasew<sup>7</sup>, Beyene Petros<sup>7</sup>, Jonathan B. Parr<sup>4,10</sup> & Jeffrey A. Bailey<sup>1,2,10</sup>✉

## The NEW ENGLAND JOURNAL of MEDICINE

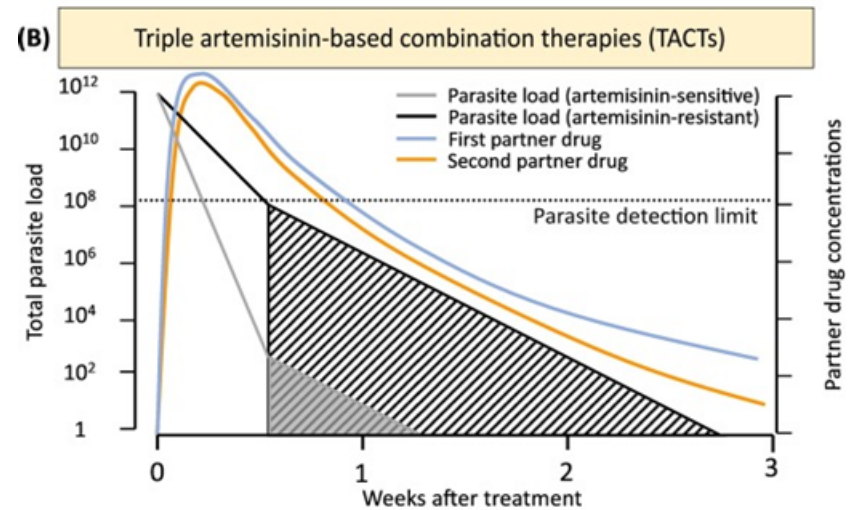
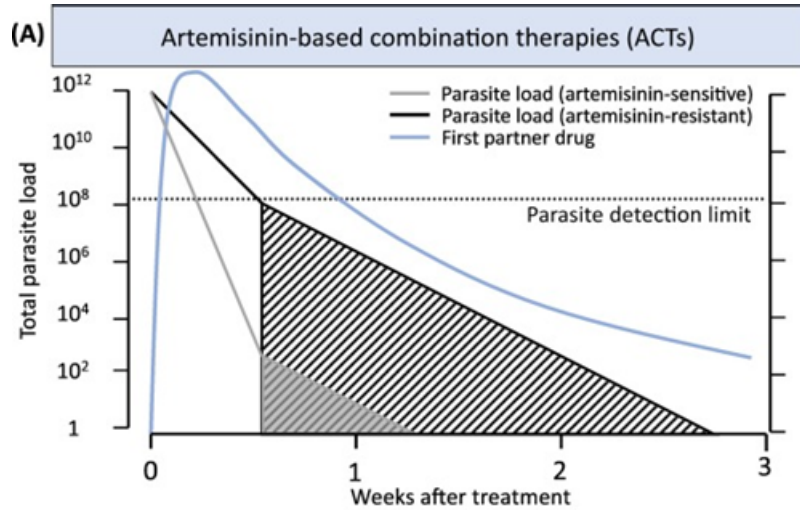
### ORIGINAL ARTICLE

## Increasing Prevalence of Artemisinin-Resistant HRP2-Negative Malaria in Eritrea

Selam Mihreteab, B.Sc., Lucien Platon, M.Sc., Araia Berhane, M.D., Barbara H. Stokes, Ph.D., Marian Warsame, M.D., Pascal Campagne, Ph.D., Alexis Criscuolo, Ph.D., Laurence Ma, B.S., Nathalie Petiot, B.S., Cécile Doderer-Lang, M.Sc., Eric Legrand, Ph.D., Kurt E. Ward, Ph.D., Assefash Zehaie Kassahun, M.D., Pascal Ringwald, M.D., Ph.D., David A. Fidock, Ph.D., and Didier Ménard, Pharm.D., Ph.D.

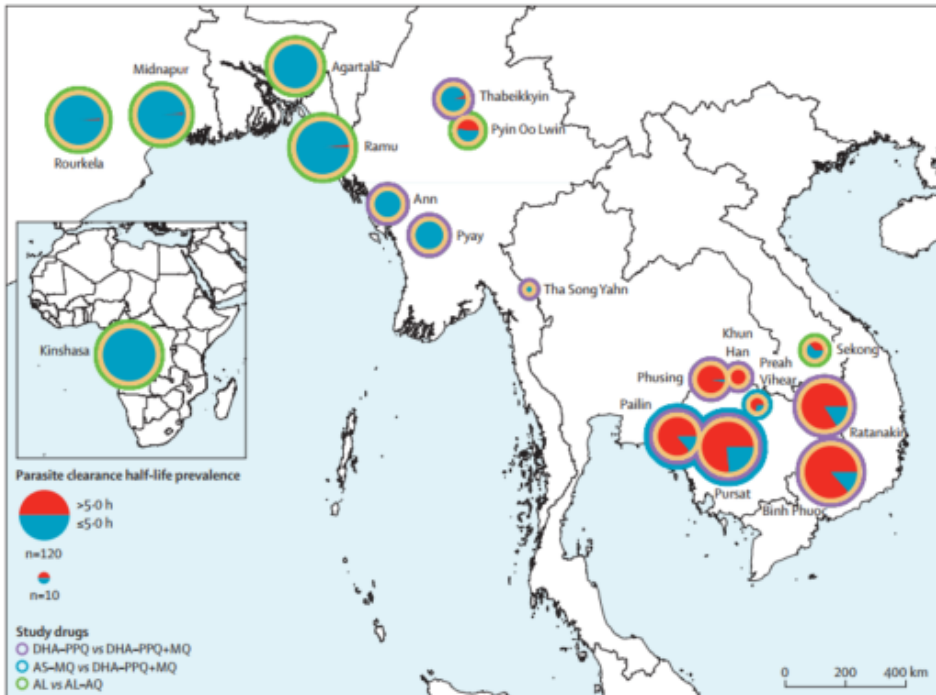


# Triple Artemisinin Combination Therapy (TACT)



If TACTs are safe, well tolerated, and efficacious, they can be deployed very quickly

# TRACII clinical trial is proof of concept of TACTs



- 1100 patients recruited
- Uncomplicated falciparum malaria with asexual parasite density of 5,000 to 200,000/ $\mu$ L
- Median age 23y (78% male)
- TACTs: **AL+AQ** and **DHA-PPQ+MQ**
- D42 PCR-corrected efficacy  $>90\%$  for TACTs
- Safe and well-tolerated

# DeTACT project

## Development of Triple Artemisinin Combination Therapies

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



DeTACT 1<sup>st</sup> Investigators' Meeting, Thailand, Jan 2019

# DeTACT project

## Development of Triple Artemisinin Combination Therapies

- ❖ **Drug development:** Produce a co-packaged presentation of two Triple Artemisinin-based Combination Therapies (TACTs)

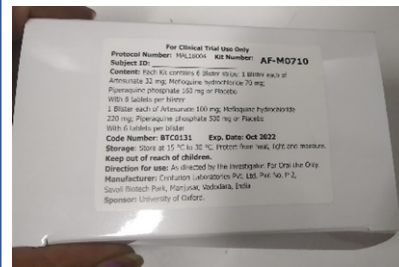
**Artemether-lumefantrine  
+ amodiaquine/placebo  
(AL+AQ/placebo)**  
*Fosun Pharma, China*



Artemether / Lumefantrine		Day 1		Day 2		Day 3	
Body weight (kg)	> 35	> 35	> 35	> 35	> 35	> 35	> 35
30-34	1.5	1.5	1.5	1.5	1.5	1.5	1.5
> 35	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Amodiaquine Hydrochloride		Day 1		Day 2		Day 3	
Body weight (kg)	> 35	> 35	> 35	> 35	> 35	> 35	> 35
20-24	1.5	1.5	1.5	1.5	1.5	1.5	1.5
> 25	1.5	1.5	1.5	1.5	1.5	1.5	1.5

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



Fosun Pharma have developed **ALAQ Fixed Dose Combination** as part of their corporate social responsibility.

# DeTACT project

## Development of Triple Artemisinin Combination Therapies

❖ **Clinical trial:** Randomised, partially-blinded, placebo-controlled clinical trial with TACTs and ACTs+placebo (n=3468) – for safety, tolerability and efficacy

### Africa

B. Faso  
DRC  
Gambia  
Guinea  
Niger  
Nigeria  
Rwanda  
Tanzania



### Asia

Bangladesh  
Cambodia

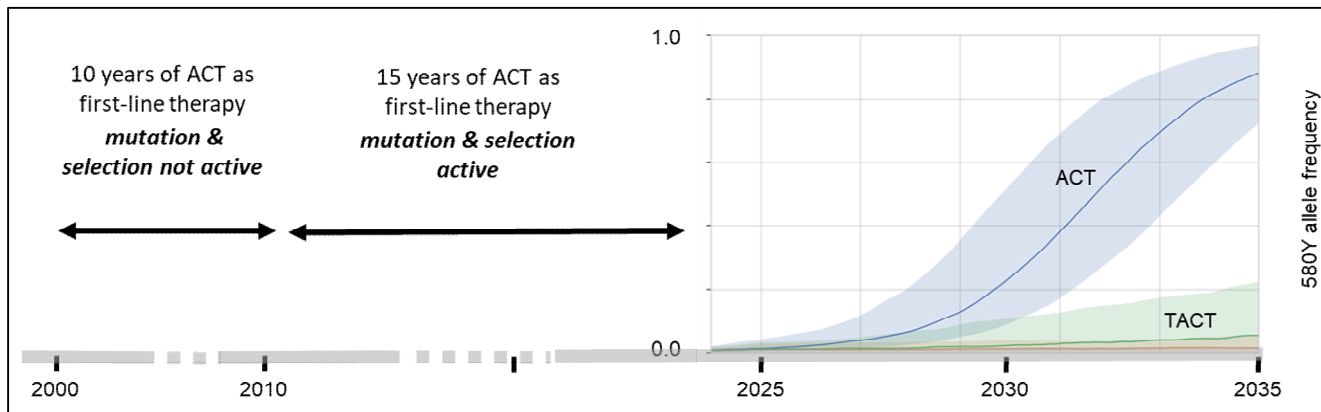
2476 enrolled by 25 Sept 2023  
Complete enrollment by Dec 2023



# DeTACT project

## Development of Triple Artemisinin Combination Therapies

- ❖ **Mathematical modelling** – Health and economic benefits of deploying TACTs in countries with different first-line therapies, transmission intensities etc.



Ricardo Aguas  
MORU



Maciej Boni  
Penn State Univ.

**Triple ACTs may delay artemisinin resistance and decrease treatment failures over 10 years**

Settings:

**ACTs:** AL, DHA-PPQ, ASAQ

**TACTs:** AL+AQ, ASMQ+PPQ

**PfPR(%):** 0.1, 1.0, 10

**Coverage (%):** 25, 50, 70

Total of 54 comparisons

(27 comparisons per TACT)



# DeTACT project

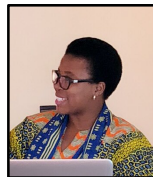
## Development of Triple Artemisinin Combination Therapies

### ❖ Bioethics & Market Positioning

Phaik Yeong Cheah  
MORU



Paulina Tindana  
University of Ghana



Jean-Bosco Ouédraogo  
INSTech



Olugbenga Mokuolu  
CENTROD



Freek de Haan



Ellen Moors  
University of Utrecht



Wouter Boon



Ethical considerations in deploying triple artemisinin-based combination therapies for malaria: An analysis of stakeholders' perspectives in Burkina Faso and Nigeria

Paulina Tindana<sup>1</sup>, Rosemonde Guissou<sup>2</sup>, Oladimeji Akeem Bolarinwa<sup>3</sup>, Fatoumata Tou<sup>4</sup>, Freek de Haan<sup>5</sup>, Mehul Dhorda<sup>6,7</sup>, Arjen M. Dondorp<sup>6,7</sup>, Chanaki Amaratunga<sup>6,7</sup>, Olugbenga Ayodeji Mokuolu<sup>8</sup>, Jean Bosco Ouédraogo<sup>9</sup>, Phaik Yeong Cheah<sup>6,7,9\*</sup>

To what extent are the antimalarial markets in African countries ready for a transition to triple artemisinin-based combination therapies?

**PLOS ONE**

Freek de Haan<sup>1\*</sup>, Oladimeji Akeem Bolarinwa<sup>2</sup>, Rosemonde Guissou<sup>3</sup>, Fatoumata Tou<sup>4</sup>, Paulina Tindana<sup>5</sup>, Wouter P. C. Boon<sup>1</sup>, Ellen H. M. Moors<sup>1</sup>, Phaik Yeong Cheah<sup>6,7</sup>, Mehul Dhorda<sup>6,7</sup>, Arjen M. Dondorp<sup>6,7</sup>, Jean Bosco Ouédraogo<sup>3,4</sup>, Olugbenga A. Mokuolu<sup>2</sup>, Chanaki Amaratunga<sup>6,7</sup>

# DeTACT project

## Development of Triple Artemisinin Combination Therapies

### ❖ Communication – Communicate findings to stakeholders and raise awareness

**Trends in Parasitology**

Opinion  
Triple Artemisinin-Based Combination Therapies for Malaria – A New Paradigm?

Rob W. van der Pluijm<sup>1,2</sup>, Chanaki Amarantunga<sup>1,2</sup>, Mehul Dhorda<sup>1,2,3</sup> and Arjen M. Dondorp<sup>2,4</sup>

CellPress  
OPEN ACCESS

**Anti-Malarial Drug Development and Diffusion in an Era of Multidrug Resistance How Can an Integrated Health Framework Contribute to Sustainable Development Goal 3?**

Freek de Haan

Ellen H.M. Moors  
DOI:10.1093/oso/9780190949501.003.0013

SCIENCE, TECHNOLOGY, AND INNOVATION  
LE GOALS  
ure, and Energy

Marian R. Chertow, and David J. Pannell

**PLOS ONE**

RESEARCH ARTICLE  
To what extent are the antimalarial markets in African countries ready for a transition to triple artemisinin-based combination therapies?

Freek de Haan<sup>1\*</sup>, Oladimeji Akeem Bolarinwa<sup>2</sup>, Rosemonde Guissoou<sup>3</sup>, Fatoumata Tou Paulina Tindana<sup>4</sup>, Wouter P. C. Boon<sup>5</sup>, Ellen H. M. Moors<sup>6</sup>, Phaik Yeong Cheah<sup>7,8</sup>, Mehul Dhorda<sup>9</sup>, Arjen M. Dondorp<sup>2</sup>, Jean Bosco Ouedraogo<sup>2,4</sup>, OluGbenga A. Mokuolu<sup>2</sup>, Chanaki Amarantunga<sup>1,2</sup>

**Wellcome Open Research**

Wellcome Open Research 2021, 6:75 Last updated: 19 AUG

STUDY PROTOCOL  
**Ethical, Regulatory and Market related aspects of Deploying Triple Artemisinin-Based Combination Therapies for Malaria treatment in Africa: A study protocol.** [version 1; peer review 2 approved]

Paulina Tindana<sup>1</sup>, Freek de Haan<sup>2</sup>, OluGbenga Ayodeji Mokuolu<sup>3</sup>, Rosemonde Guissoou<sup>4</sup>, Oladimeji Akeem Bolarinwa<sup>5</sup>, Jean Bosco Ouedraogo<sup>6,4</sup>, Fatoumata Tou<sup>6</sup>, Wouter P.C. Boon<sup>6,2</sup>, Ellen H.M. Moors<sup>2</sup>, Arjen M Dondorp<sup>6,2</sup>, Mehul Dhorda<sup>7,8</sup>, Chanaki Amarantunga<sup>7,8</sup>, Phaik Yeong Cheah<sup>7,8</sup>

**MORU** Tropical Health Network

**Ethical and market positioning considerations of deploying triple artemisinin-based combination therapies in African countries – perspectives from Burkina Faso and Nigeria**

A study conducted under the auspices of the Development of Triple Artemisinin-based Combination Therapies (DeTACT) project funded by UK Aid from the Foreign, Commonwealth & Development Office (FCDO) of the United Kingdom

A webinar to disseminate the results from the DeTACT bioethics and market positioning studies in Burkina Faso and Nigeria (all are welcome, no registration required)

**SPEAKERS**

Date: 14 December, 10:00-12:00 GMT  
Place: <https://bit.ly/DeTACTWebinar>  
Chair: OluGbenga Mokuolu  
Co-Chair: Chanaki Amarantunga

Wellcome – OluGbenga Mokuolu  
Current status of antimalarial drug resistance – Arjen Dondorp  
The Development of Triple Artemisinin-based Combination Therapies (DeTACT) project – Chanaki Amarantunga  
The DeTACT clinical trial – Mehul Dhorda  
To what extent are African antimalarial markets ready to transition to triple ACTs? – Freek de Haan & Akeem Bolarinwa  
Ethical considerations in deploying triple ACTs for malaria in African countries – Paulina Tindana, Rosemonde Guissoou & Phaik Yeong Cheah  
Q&A session  
Closing remarks – Jean Bosco Ouedraogo

Di Paulina Tindana  
University of Ghana

Prof OluGbenga Mokuolu  
University of Ife

Assoc Prof Akeem Bolarinwa  
University of Ife

Prof Jean Bosco Ouedraogo  
IRSS, Burkina Faso

Rosemonde Guissoou  
IRSS, Burkina Faso

Prof Arjen Dondorp  
Di Chanaki Amarantunga  
Di Mehul Dhorda  
Assoc Prof Phaik Yeong Cheah  
Freek de Haan  
University of Utrecht

Mahidol Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand

Contents lists available at ScienceDirect

**Environmental Innovation and Societal Transitions**

ELSEVIER journal homepage: [www.elsevier.com/locate/eist](http://www.elsevier.com/locate/eist)

Survey  
Market Formation in a Global Health Transition

Freek de Haan<sup>a,\*</sup>, Ellen H.M. Moors<sup>a</sup>, Arjen M. Dondorp<sup>b</sup>, Wouter P.C. Boon<sup>a,b</sup>

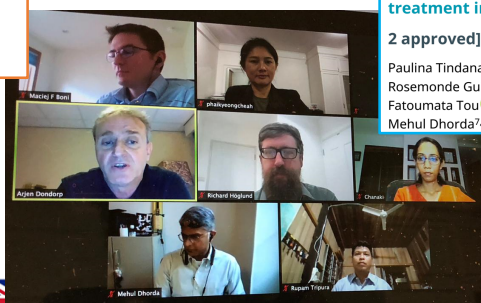
de Haan et al. BMC Public Health (2022) 22:864  
<https://doi.org/10.1186/s12889-022-13212-x>

**BMC Public Health**

RESEARCH Open Access

Expert perspectives on the introduction of Triple Artemisinin-based Combination Therapies (TACTs) in Southeast Asia: a Delphi study

Freek de Haan<sup>1,2</sup>, Wouter P.C. Boon<sup>1</sup>, Chanaki Amarantunga<sup>2</sup> and Arjen M. Dondorp<sup>2</sup>



**PLOS ONE**

RESEARCH ARTICLE  
Ethical considerations in deploying triple artemisinin-based combination therapies for malaria: An analysis of stakeholders' perspectives in Burkina Faso and Nigeria

Paulina Tindana<sup>1</sup>, Rosemonde Guissoou<sup>2</sup>, Oladimeji Akeem Bolarinwa<sup>3</sup>, Fatoumata Tou<sup>4</sup>, Freek de Haan<sup>5</sup>, Mehul Dhorda<sup>6</sup>, Arjen M. Dondorp<sup>6</sup>, Chanaki Amarantunga<sup>7,8,9,10</sup>, OluGbenga Ayodeji Mokuolu<sup>11</sup>, Jean Bosco Ouedraogo<sup>12</sup>, Phaik Yeong Cheah<sup>13,14,15,16,17,18</sup>



**Malaria Journal**

COMMENTARY Open Access

Deploying triple artemisinin-based combination therapy (TACT) for malaria treatment in Africa: ethical and practical considerations

Paulina Tindana<sup>1</sup>, Freek de Haan<sup>2</sup>, Chanaki Amarantunga<sup>3,4</sup>, Mehul Dhorda<sup>5,6</sup>, Rob W. van der Pluijm<sup>6,7</sup>, Arjen M. Dondorp<sup>8,9</sup> and Phaik Yeong Cheah<sup>10</sup>



# DeTACT project



- ❖ Drug development
- ❖ Clinical trial
- ❖ Mathematical modelling
- ❖ Bioethics
- ❖ Market positioning

## Extension:

## ALAQ deployment readiness in Rwanda & Uganda

- ❖ Communications
- ❖ Individual patient data  
meta-analysis



# FD-TACT project

*(expected to begin in 2024)*

*Fixed dose combination (FDC) of  
artemether-lumefantrine-amodiaquine (ALAQ)*

- ❖ **ALAQ FDC – development**
- ❖ **ALAQ FDC – clinical trial**
- ❖ **ALAQ FDC – prequalification**
- ❖ **ALAQ FDC – commercialization**
- ❖ **Human rights and health equity**

