

# Optimising dosing of antimalarials to prevent drug resistance

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# Antimalarial: Efficacy and Resistance

**Antimalarial Resistance**: The ability of the parasite to survive or multiple in concentrations of drug that would otherwise kill it

## Drug Factors

- Pharmacodynamics: PRR, Stage specificity
- Pharmacokinetics: ADME, DD Interactions
- Dosing strategy: banding
- Tolerability
- Drug quality and formulations

## Parasite Factors

- Biomass
- Sequestration
- Mixed Species
- Staging
- Reinfection, Relapse
- **Resistance**

**Efficacy**

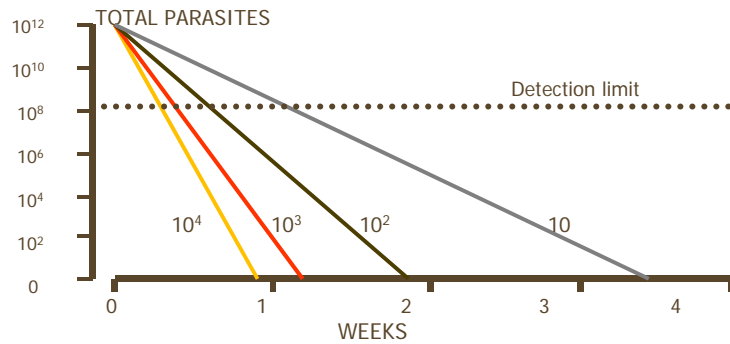
## Host Factors

- Innate and Acquired Immunity
- Comorbidities: coinfection, GI
- Nutrition
- Pharmacogenomics: CYP2d6
- Treatment seeking behaviour
- Adherence

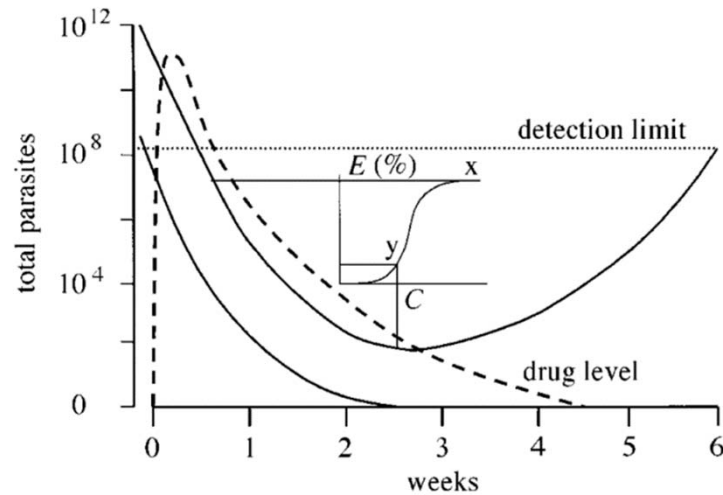
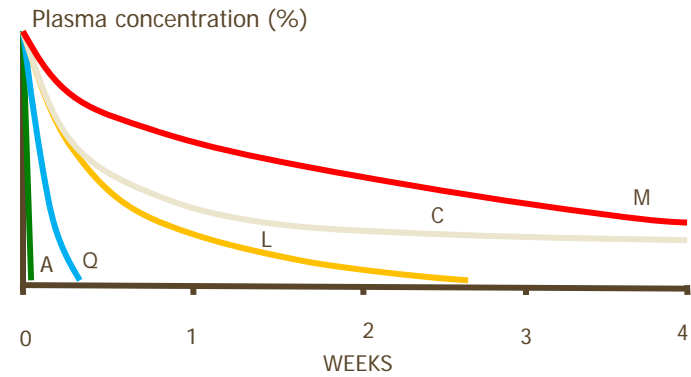
**High Drug Efficacy:** Dosing > Absorption > Immunity > Resistance  
**Declining Efficacy:** Resistance > Absorption > Dosing > Immunity

# Parasite Killing

## Pharmacodynamics



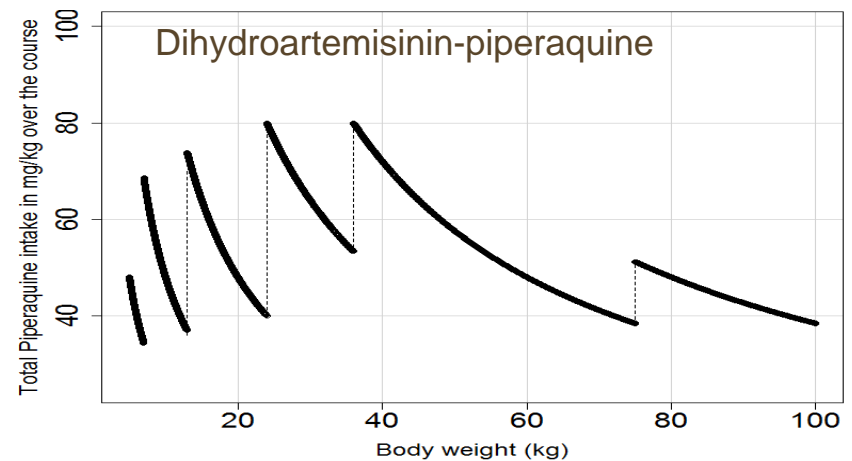
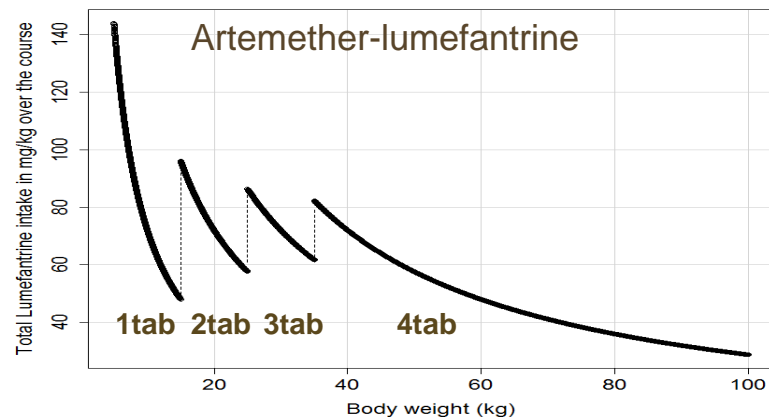
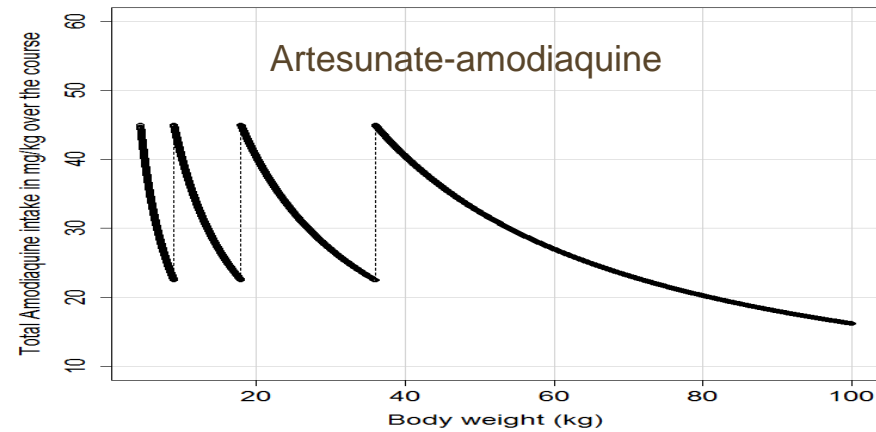
## Pharmacokinetics



NJ White Journal of Clinical Investigation 2004

# What Dose Should We Give ?

**Target Dose:**  
Uniform or age stratified



# Dose impact study groups



## Artemether-lumefantrine (AL):

66 studies  
15,214 patients  
377 failures

## Artesunate-amodiaquine (AS-AQ):

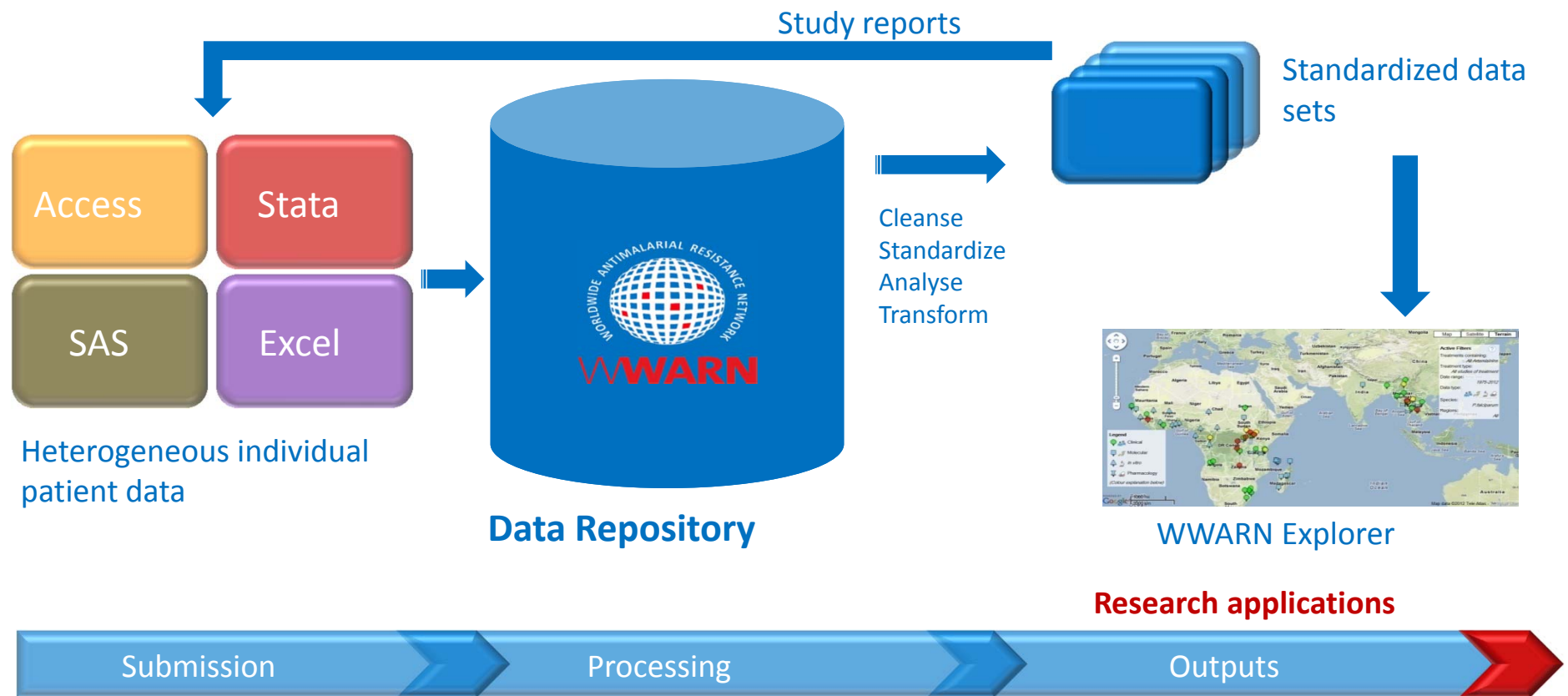
43 studies  
9,106 patients  
295 failures

## DHA-piperaquine (DHA-PIP):

26 studies  
7,072 patients  
136 failures

A priori Statistical Plan: <http://www.wwarn.org/partnerships/study-groups/dha-pqp-dose-impact-study-group>  
Publication Policy: <http://www.wwarn.org/sites/default/files/PublicationPolicy.pdf>

# Data collection and standardisation



# DHA - Piperazine

# DHA-Piperaquine efficacy

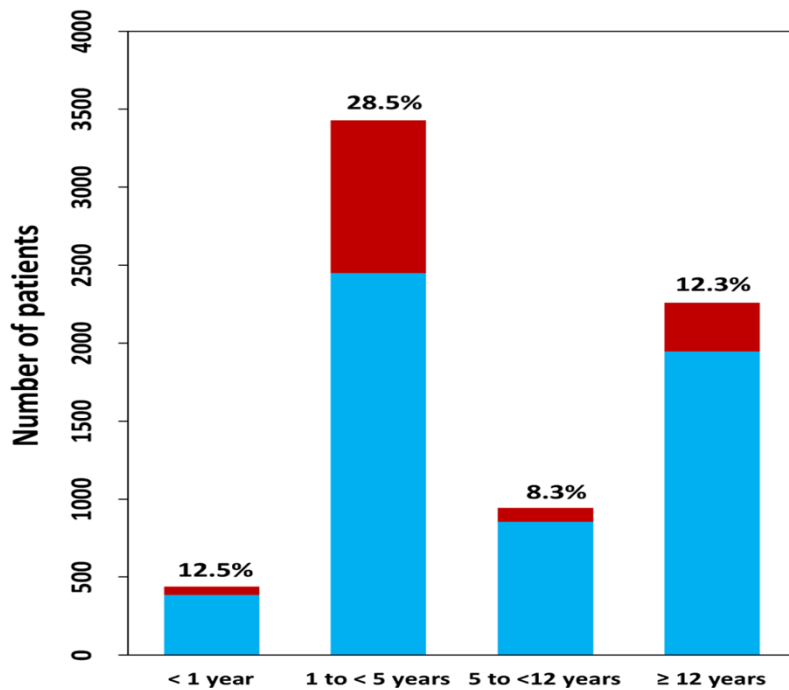
## The Effect of Dosing Regimens on the Antimalarial Efficacy of Dihydroartemisinin-Piperaquine: A Pooled Analysis of Individual Patient Data

The WorldWide Antimalarial Resistance Network (WWARN) DP Study Group\*

### DHA-piperaquine (DHA-PIP):

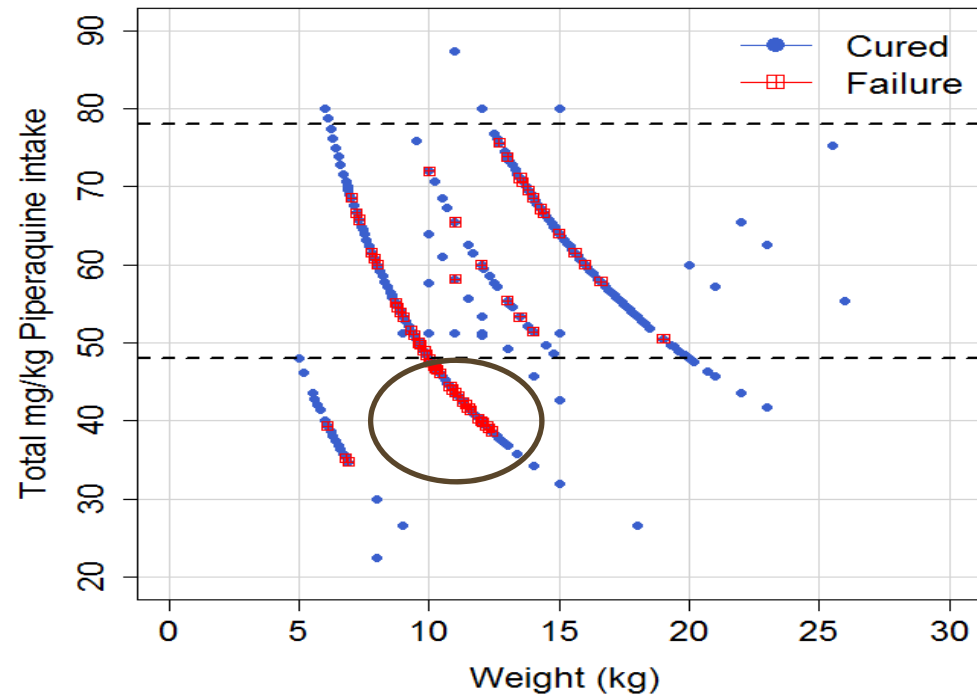
26 studies  
7,072 patients  
136 failures

## Dosing of Piperaquine



Proportion of patients below the WHO recommended the therapeutic range (48 -78 mg/kg) for piperaquine

Young children administered suboptimal doses





# Dosing implications for DHA-Piperaquine efficacy

	Kaplan-Meier Survival Estimates		
	Day28 n=5371	Day42 n=3476	Day63 n=1209
<b>Overall</b>	98.8 %	97.5 %	96.8 %
<b>Age group</b>			
<1 yrs	-	98.0 %	-
1-<5 yr	98.0 %	<b>95.5 %</b>	<b>94.0 %</b>
5-<12 yrs	99.2 %	98.8 %	-
>=12 yrs	99.9 %	99.4 %	98.7 %
<b>Region</b>			
Africa	98.5	<b>96.0</b>	<b>94.0</b>
Asia	99.3	98.9	98.4

## Patients with low DHA Dose ...

Greater Risk of Parasitaemia on Day 3

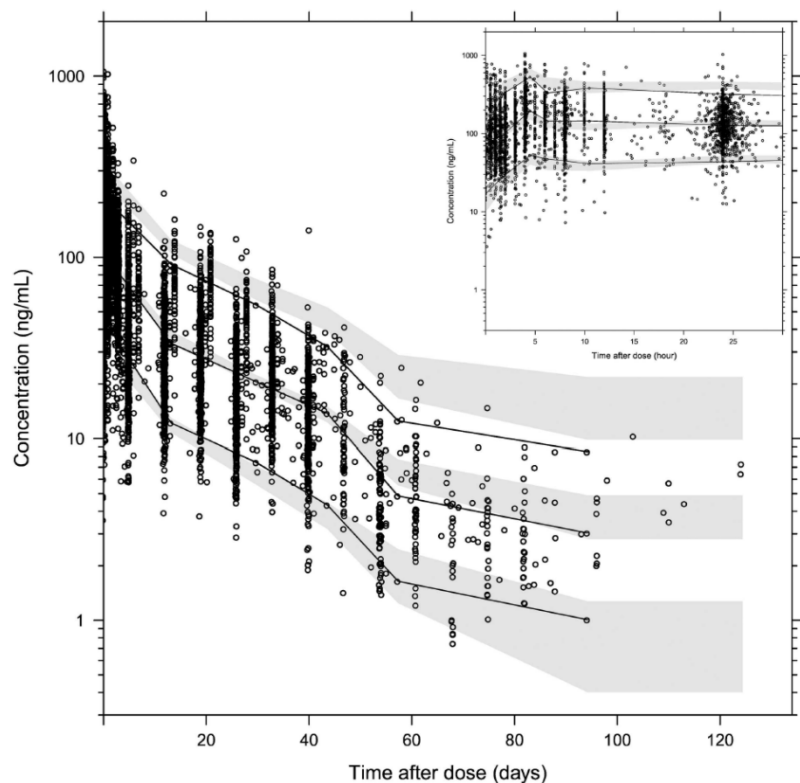
Greater Risk of Gametocyte Carriage on day 7

11 studies  
8776 samples  
728 individuals

RESEARCH ARTICLE

# Population Pharmacokinetic Properties of Piperaquine in Falciparum Malaria: An Individual Participant Data Meta-Analysis

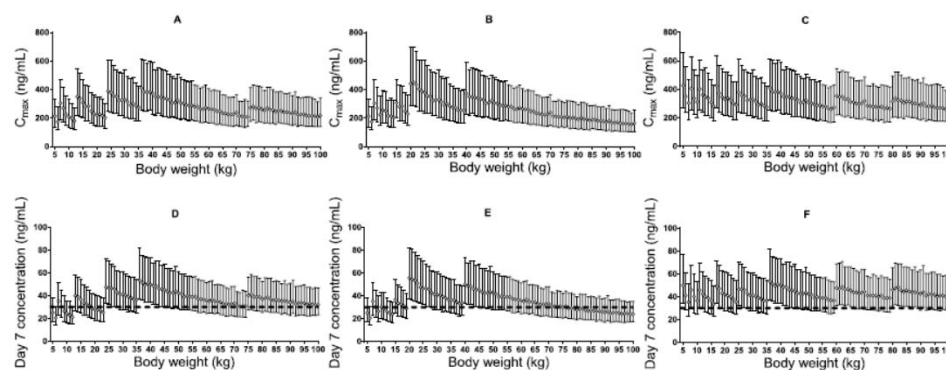
Richard M. Hoglund<sup>1,2,3</sup>, Lesley Workman<sup>1,4</sup>, Michael D. Edstein<sup>5</sup>, Nguyen Xuan Thanh<sup>6</sup>, Nguyen Ngoc Quang<sup>7</sup>, Issaka Zongo<sup>8,9</sup>, Jean Bosco Ouedraogo<sup>8</sup>, Steffen Borrmann<sup>10,11</sup>, Leah Mwai<sup>10,12</sup>, Christian Nsanzabana<sup>1,3</sup>, Ric N. Price<sup>1,3,13</sup>, Prabin Dahal<sup>1,3</sup>, Nancy C. Sambol<sup>14</sup>, Sunil Parikh<sup>15</sup>, Francois Nosten<sup>3,16</sup>, Elizabeth A. Ashley<sup>16</sup>, Aung Pyae Phyo<sup>16</sup>, Khin Maung Lwin<sup>16</sup>, Rose McGready<sup>3,16</sup>, Nicholas P. J. Day<sup>2,3</sup>, Philippe J. Guerin<sup>1,3</sup>, Nicholas J. White<sup>2,3</sup>, Karen I. Barnes<sup>1,4</sup>, Joel Tarning<sup>1,2,3\*</sup>



## Sigma-Tau

## Holley-Cotec

## Revised



**Fig 5. Stochastic simulations of dose regimens.** Maximum plasma piperaquine concentration (A–C) and day 7 plasma piperaquine concentration (D–F) after Sigma-Tau’s recommended dosing (left panels), Beijing Holley-Cotec’s recommended dosing (middle panels), and the revised dose regimen (right panels). Circles represent the median values, and vertical lines represent the 25th to 75th percentiles of simulated concentrations. The dashed line indicates the previously defined venous plasma piperaquine day 7 concentration threshold value for therapeutic success of 30 ng/ml [35].

doi:10.1371/journal.pmed.1002212.g005

# Artemether - Lumefantrine

# Artemether-Lumefantrine

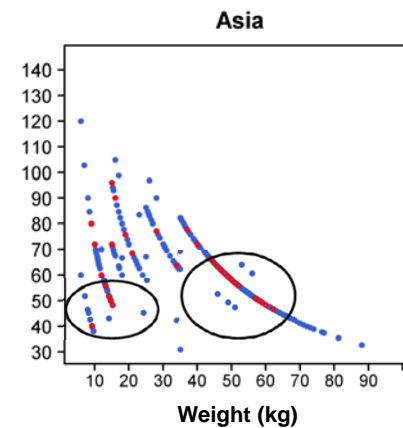
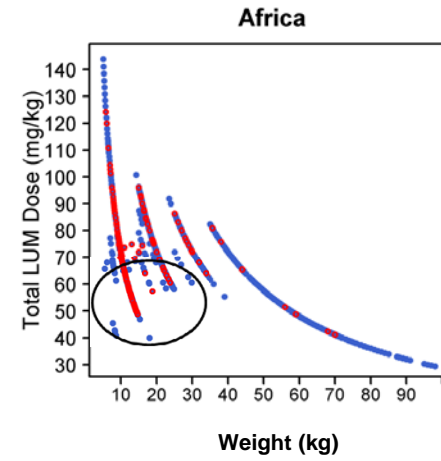
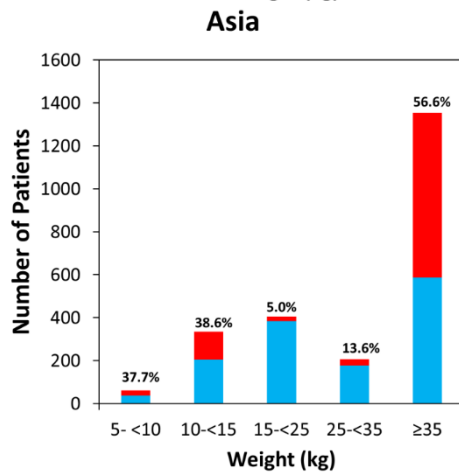
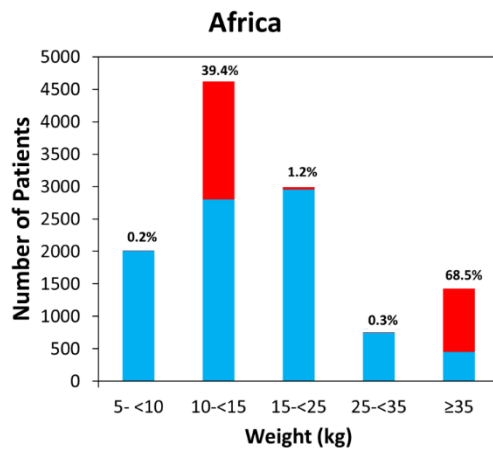
The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data

Worldwide Antimalarial Resistance Network (WWARN) AL Dose Impact Study Group\*

Lancet Infect Dis 2015

66 studies  
15,214 patients  
377 failures

Proportion of patients below the WHO recommended the therapeutic range (60 mg/kg) for lumefantrine



# Dosing implications for AL efficacy

		Kaplan-Meier Survival Estimates	
		N	
		Day28 n=11,923	Day42 n=4,279
Overall		97.6 %	96.0 %
<u>Age group</u>			
<1 yrs		803	97.0 %
1-3 yrs	underweight	679	94.3 %
1-3 yrs	weight OK	3,073	96.8 %
3-5 yrs		3,352	97.9 %
5-<12 yrs		2,939	98.4 %
≥12 yrs		3,001	98.9 %
<u>Region</u>			
Africa		11,674	97.5 %
Asia		2,306	98.0 %
S America		159	99.4 %

## Patients with low artemether daily Dose ...

Greater Risk of Parasitaemia on Day 1

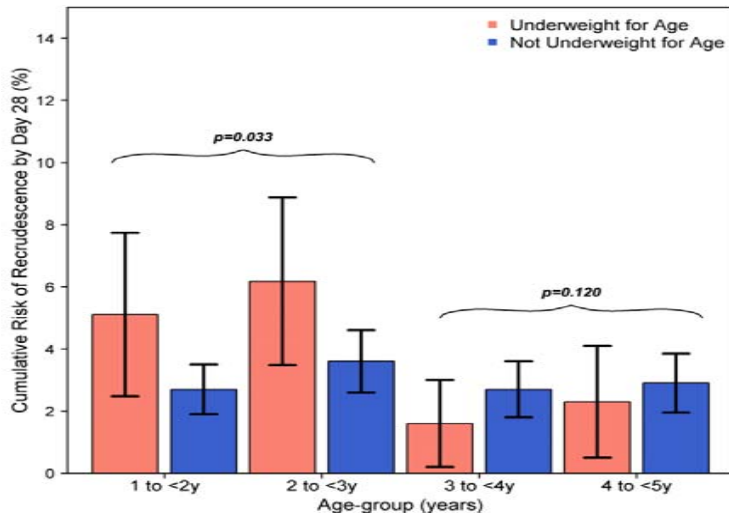
## Patients with low artemether total Dose ...

Greater Risk of Gametocyte Carriage on day 14

# Artemether-Lumefantrine

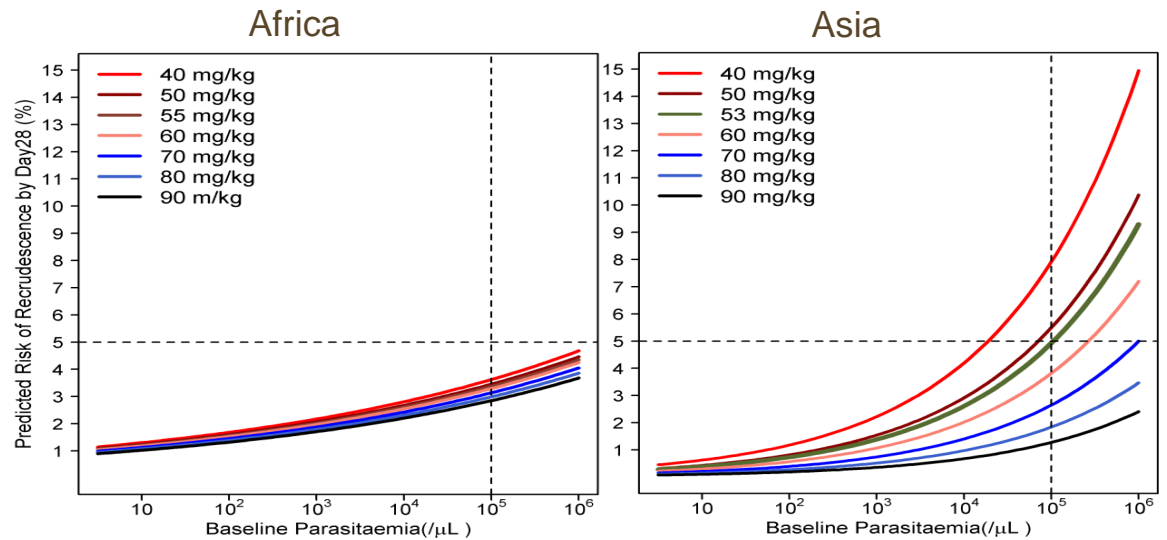
## AL study group

Africa



Malnutrition associated with treatment failure in Africa

LUM dose associated with treatment failure in Asia



WWARN AL study group, submitted

# *P. vivax* and Chloroquine

# The Vivax Surveyor – Literature Review



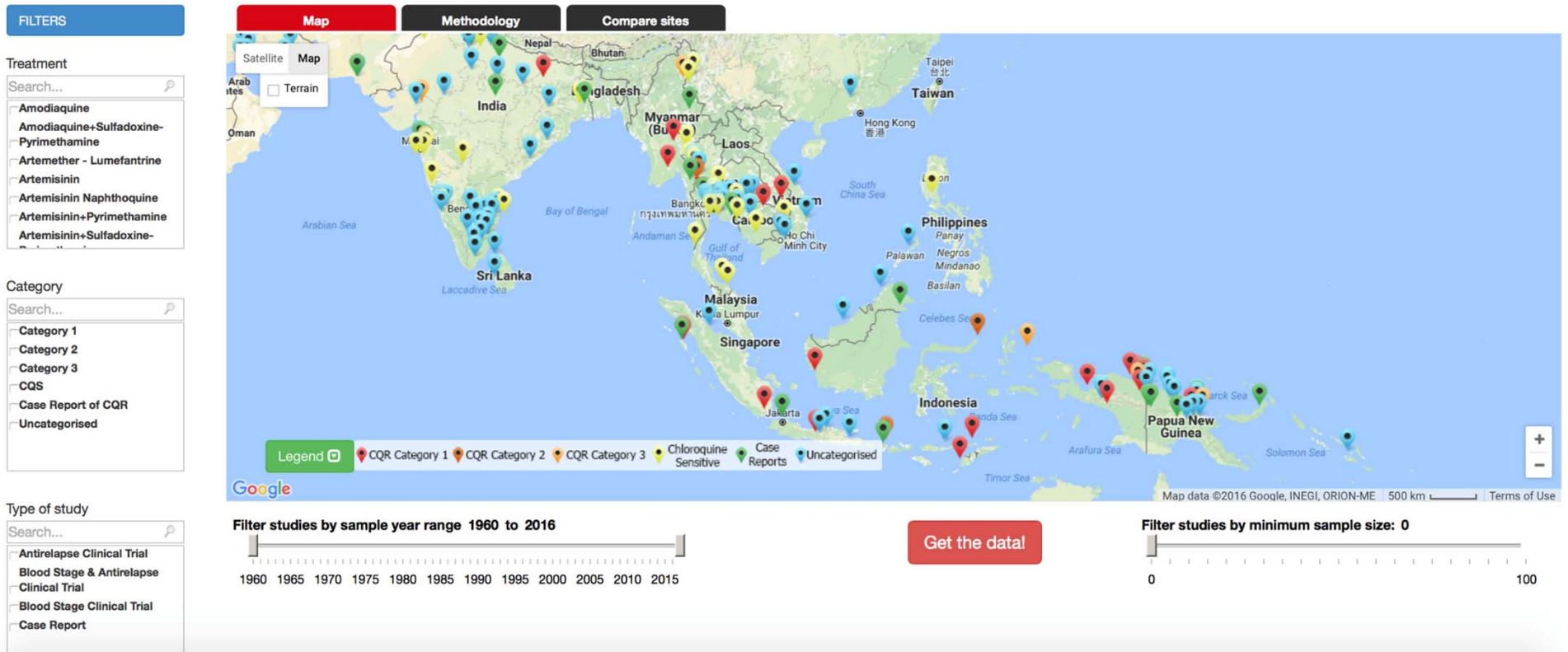
WWARN

Home

[www.wwarn.org/vivax/surveyor](http://www.wwarn.org/vivax/surveyor)

Vivax Surveyor

Mapping vivax drug studies



## Systematic Literature Review

- Prospective Clinical Trials since 1960
- 237 clinical trials, 428 treatment arms, 338 study sites
- 78,401 patients, 27 case reports

## Global extent of chloroquine-resistant *Plasmodium vivax*: a systematic review and meta-analysis

Ric N Price, Lorenz von Seidlein, Neena Valecha, Francois Nosten, J Kevin Baird, Nicholas J White

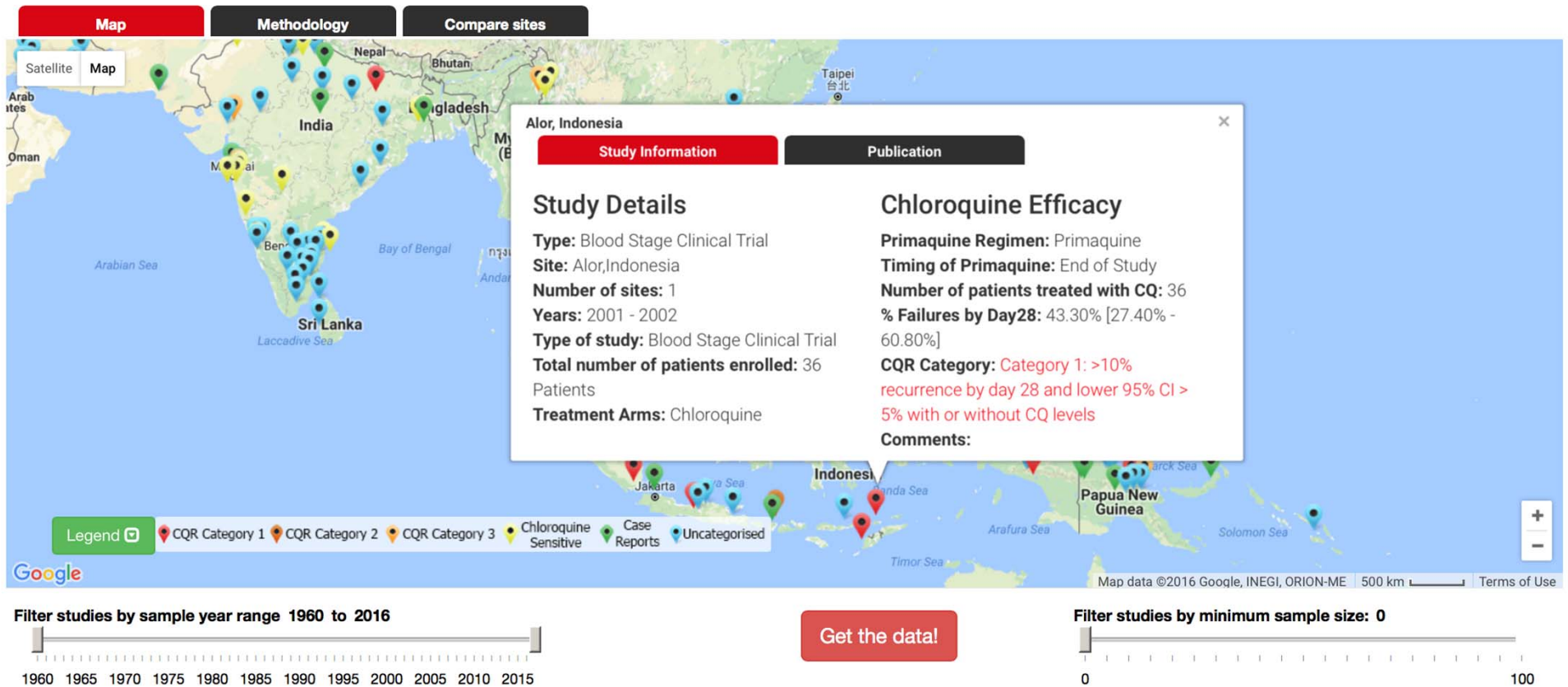
*Lancet Infect Dis* 2014



# The Vivax Surveyor – Literature Review

## Vivax Surveyor

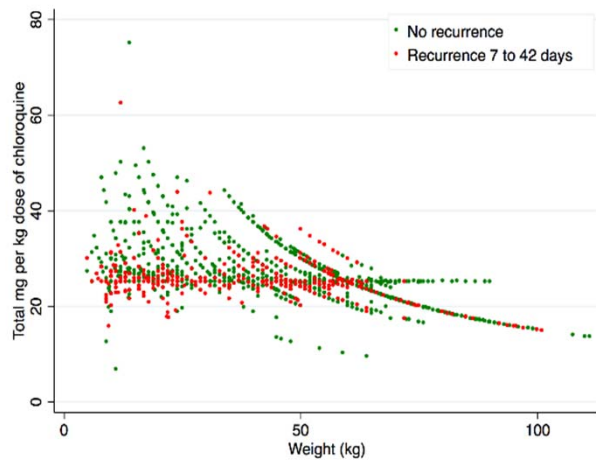
Mapping vivax drug studies



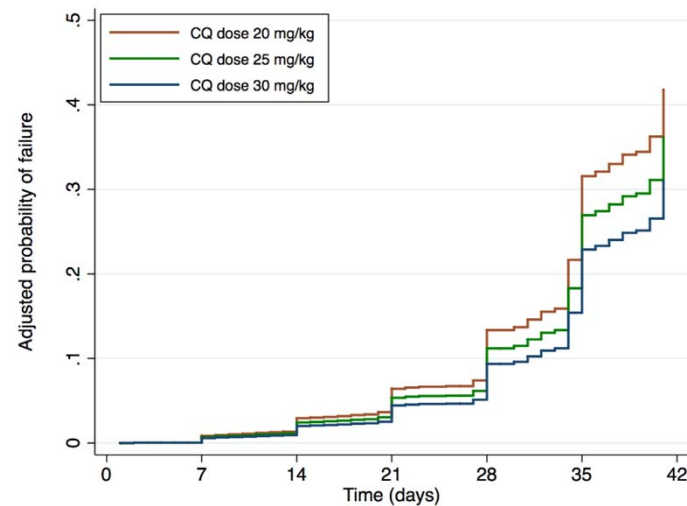
[www.wwarn.org/vivax/surveyor](http://www.wwarn.org/vivax/surveyor)

# Have we got the dose right ?

**Individual Pooled Analysis:** 39 studies, 5,413 patients with Pv treated with Cq



35% of patients have a CQ dose < 25mg/kg



For every 5 mg/kg dose increase:

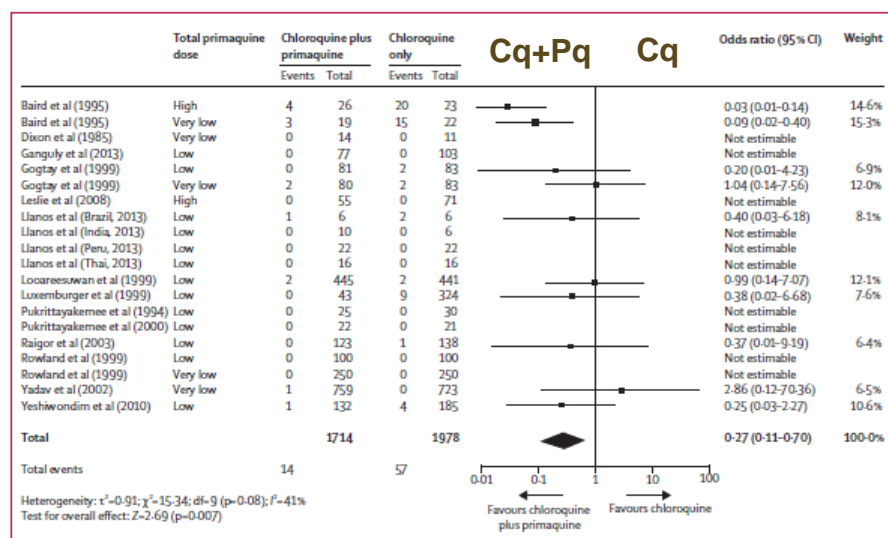
**AHR = 0.83 (0.71 – 0.98)**

Increasing target dose of CQ to 30mg/kg in young children would prevent 35% of recurrences



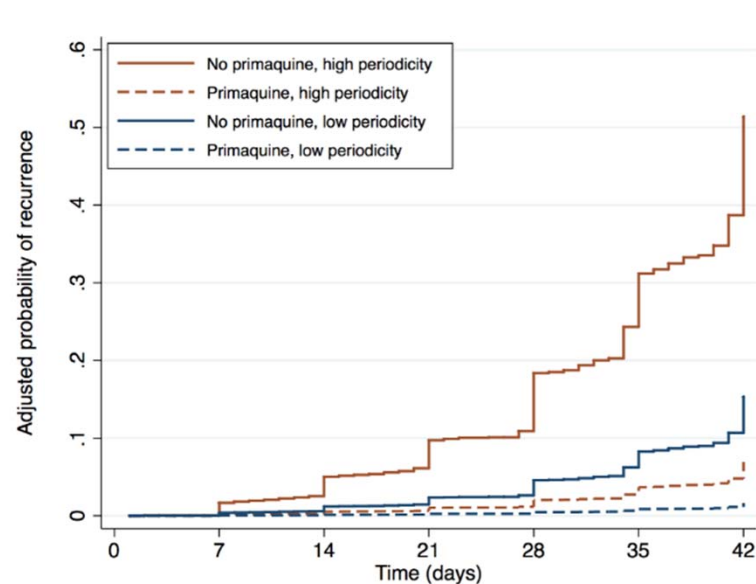
# Coadministration of Primaquine

## Literature Review



**AHR: 0.27 (0.11-0.70),  $p < 0.001$**

## Pooled Analysis



Additional Primaquine:

**AHR: 0.09 (0.05 – 0.17)**

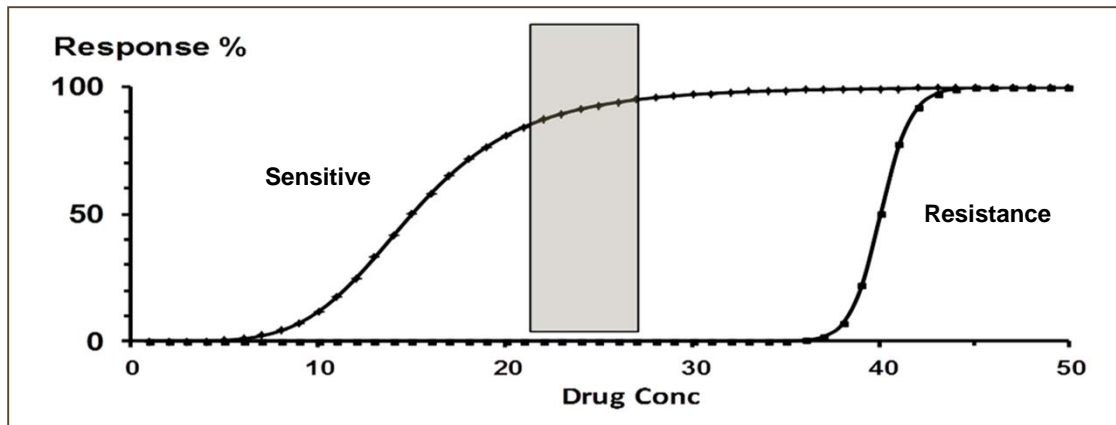


# Conclusions

- Treatment failure doesn't equate to resistance, but it is the driving force
  - Its vital to get the basics right !**
  - ➔ Dose - Treatment Regimen – Delivery
- Children are particularly vulnerable to a wide range of doses
  - ➔ Need for paediatric formulations
- Dose adjustment or coadministration with an additional drug can improve drug efficacy and prevent drug resistance

# Does it matter ?

- **200 million treatments**
  - ~50% aged 1-5 yrs
  - Improving efficacy by 4%, prevents 4.2 million infections
- **“Falling off the dose response curve”**





# WWARN Collaborator Network



BILL & MELINDA  
GATES foundation



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PhD Student  
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- Ingrid van der Broek
- Ishag Adam
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- Issaka Zongo
- Issiaka Soulama
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